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The purpose of this project is to refine and test a "visual neural network," combined with a mammographic database, for its ability too help radiologists reduce the number of benign biopsies in mammographic screening without increasing the number of missed cancers. We refer to this as a "mapped database diagnostic system." The unique features of this system are a)its exploitation of a clinically proved database of mammograms for enhanced diagnosis, b)automatic selection of highly discriminating mammographic features, and c) a two-dimensional "relational map" for enhanced browsing through the mammographic database.
Years 1 and 2 of this project will be devoted primarily to retrospective studies, Years 3 and 4 primarily to clinical studies. In Year 1, reported here, we completed our tests of the mapped database diagnostic system on regions of interest containing microcalcifications. In these tests four radiologists, acting independently on 100 ROIs, recommended biopsies for 18, 15, 28, and 18 benign ROIs, and misdiagnosed cancers in 11, 12, 7, and 8 ROIs, respectively. Interaction with the mapped-database system reduced the numbers of benign biopsies to 11, 8, 18, and 10 cases, and the numbers of misdiagnosed cancers to 8, 7, 4, and 3 cases, respectively. Statistical analysis indicated that 3 of the radiologists achieved significant improvements at $p \leq 0.02$; the fourth achieved an improvement at $p \leq 0.07$. These results suggest that radiologists using this system can statistically significantly reduce the numbers of benign biopsies and misdiagnosed cancers. The enhanced diagnostic benefits seems to apply to mammographically certified radiologists over a wide range of capabilities and durations of post-certified experience.

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FOREWORD

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INTRODUCTION

The purpose of this project is to refine a "visual neural network," combined with a mammographic database, and test it for its ability to help radiologists reduce the number of benign biopsies in mammographic screening without increasing the number of missed cancers. We refer to this as a "mapped database diagnostic system." The unique features of this system are a) its exploitation of a clinically proved database of mammograms for enhanced diagnosis, b) automatic selection of highly discriminating mammographic features, and c) a two-dimensional "relational map" for enhanced browsing through the mammographic database.

Years 1 and 2 of this project will be devoted primarily to retrospective studies, Years 3 and 4 primarily to clinical studies.

BODY

Task 1. Devise, construct, and test an initial lesion detector for mammography (months 1-12).

a. Modify earlier software for detection of microcalcifications to admit additional types of lesions, including masses, stellate lesions, asymmetries and architectural abnormalities. (months 1-2)
b. Construct new algorithms for mass detection based on known techniques, such as Gaussian derivative operators, difference of Gaussians, Laws texture features, density-weighted contrast enhancement, and Laplacian-Gaussian edge detection. Incorporate this algorithm in the algorithm for microcalcifications detection. Test algorithm on digital image data obtained in Task 3b. (months 1-6)
c. Construct new algorithms for detection of asymmetries and architectural distortions. This detector may be based on recent work on model-based analysis of mammograms. Incorporate this detector in the algorithm for microcalcification and mass detection. Test algorithm on image data obtained in Task 3h. (months 7-12)

In accordance with Task 1a and Task 1b, we developed a lesion detector for masses, and tested it successfully on a test set of regions of interest from the University of South Florida (USF) database. Task 1c will be postponed to Year 2 or Year 3.

Task 2. Construct advanced lesion detector (months 4-9).

a. The panel of radiological fellows will label each of the candidate lesions produced by the initial lesion detector as *mass, microcalcifications, asymmetry, architectural distortion,* or *nonlesion.* (months 4-5)
b. Build an algorithm for extracting about 40 morphological features from the candidate lesions based on earlier work [30]. (months 4-7)
c. Build a genetic algorithm for selecting no more than 10 morphological features for use in a lesion classifier. The error rate of a *k*-nearest-neighbor classifier will be the penalty function for this genetic algorithm in accordance with [25]. The same genetic process that selects the features will choose the value of k. (months 8-9)
d. Combine the *k*-nearest-neighbor classifier with the initial lesion detector to form an advanced lesion detector. (month 10)

The "advanced lesion detector" in Task 2d was combined with the neural classifier of Task 5, described below. Tasks 5a and 5b were implemented this year, five months ahead of schedule. We plan to implement Task 5c in month 17, as originally scheduled.

Task 3. Collect and organize a database of proven mammographic regions of interest (months 1-6, 12-24) from at least 400 subjects, restricting the lesions to microcalcifications and masses.

a. Collect film mammograms from at least 400 subjects, restricting the lesions to microcalcifications and masses. (The masses will include stellate lesions.) Add teaching files if possible. Include films from King-Drew Medical Center (KDMC) and from University of California at Los Angeles (UCLA). (months 1-2)
b. Digitize all films on Lumiscan 85 film scanner at a 50-micron pixel width. Save all digitized mammograms on compact disc. (month 2)
c. On each mammogram find one or more lesions, using the advanced lesion detector of Task 2. Enclose one or more of these lesions in a 512×512-pixel or a 1024×1024 – pixel square. We refer to this square as a region of interest (ROI). (months 3-4)
d. Print hard copies of all of the digitized ROIs collected in Task 3c. Each radiologist on this project will partition the ROIs into groups of medically and perceptually similar ROIs. A medically or visually descriptive label will identify each group. We refer to these as *perceptual similarity groups*. The radiologists will form a consensus on a final grouping and labeling of these groups. (Month 5)
e. Each radiologist will construct a dissimilarity matrix for these groups. Each element of this matrix will contain the radiologist's subjective estimate of the dissimilarity of the corresponding two groups on a scale from 0 to 5, 0 designating identity, and 5 designating extreme dissimilarity. (Month 5)
f. Label the resulting ROI as one of {mass, calcification, asymmetry, architectural distortion} and as one of {benign, malignant}. (Month 5)
g. Partition the database of ROIs into D and T, in a manner so that the distributions of types of abnormalities and perceptual similarity groups in D and T are similar. (Month 6)

We collected and organized a database of full-field mammograms and proven regions of interest (ROIs). This database consisted of about 1000 cases from the University of South Florida (USF), 160 cases from the King-Drew Medical Center (KDMC), and 10 cases from the Iris Cantor mammography center at the University of California at Los Angeles (UCLA). The cases were described on a report form designed jointly by members of this project at KDMC and UCLA. A copy of this form is provided in Appendix 1. The radiology fellows in our project circumscribed each observed abnormal region by a rectangle aligned with the horizontal and vertical axes. Thus we completed Tasks 3a, 3b, and 3c. Tasks 3d, 3e, 3f, and 3g have been postponed to Year 2.

Task 4. Construct a graphical user interface for interacting with the two-monitor high-resolution display and the control monitor. Include a high-resolution simulated square magnifying glass that shows a window excised from the 4000 × 5000-pixel array produced by the scanner. Include a brightness inversion capability. Include a brightness control and a contrast control. (months 14-15). This Task was completed 3 months ahead of schedule.

Task 5. Construct and train a visual neural classifier and a relational map. (months 16-17)

a. Extract the set of features *F2* from the design set *D*. Use the genetic algorithm *G2* to find a set of reduced-dimensionality features for analyzing the ROIs. Using these reduced-dimensionality features for design set *D*, construct a database *K* of labeled reduced-dimensionality feature vectors for training the visual neural classifier. (month 16)
b. Construct an initial 5-layer visual neural network and a relational map, based on the design principles described in [18-20]. (month 17)
c. Train this neural network using the design set *K* to preserve perceptual similarity grouping and benign-malignant separation in the relational map. (month 17)

Tasks 5a and 5b were completed ahead of schedule. The function of the 5-layer neural network in Task 5b was expanded to include the "advanced lesion detector" of Task 2d.

Task 6. Construct a mapped database system (originally called "neurodatabase system,") consisting of a graphical user interface, a relational map, the visual neural classifier, and the proven mammographic database. (month 17)

This Task was completed successfully, 5 months ahead of schedule.

ADDITIONAL ACTIVITIES:

1. We carried out an ROC analysis of the 4 unaided radiologists, the 4 aided radiologists, and the computer alone for our earlier retrospective test of our mapped database diagnostic system. The results of this test show that radiologists may achieve statistically significantly reductions in the numbers of benign biopsies and misdiagnosed cancers with the aid of a mapped database of proved mammographic ROIs. This test is described in a paper published in the June 2000 issue of Academic Radiology. A cop y of this paper is given in Appendix 2.

2. We devised and implemented a novel computer architecture for our mapped database diagnostic system that will facilitate incorporating this system in multisatellite teleradiology systems. This architecture includes a Java-expressed user interface that can be tied to a wide variety of remotely sited workstations, each with its distinct operating system. We plan to present this architectural concept at the 2001 SPIE International Symposium on Medical Imaging in San Diego.

RELEVANCE OF THE ABOVE WORK TO THE ORIGINAL HYPOTHESIS.

The following is our original hypothesis: *Compared to an unaided radiologist a neurodatabase diagnostic system assisting a radiologist in mammographic screening can significantly reduce both the incidence of negative biopsies as well as the incidence of missed cancers.*

The published paper (given in Appendix 2) shows the validity of this hypothesis when the image data are restricted to regions of interest containing either microcalcifications or normal tissue.

KEY RESEARCH ACCOMPLISHMENTS

- Constuction of relational map for mammographic masses
- Determination of discriminating features for mass detection
- Construction of mass detector
- Testing of mass detector
- Demonstration of statistical improvement of database-aided reader over unaided reader with respect to both misdiagnosed breast cancers and falsely detected breast cancers.
- Design and construction of platform-independent architecture for multisatellite remotely aided diagnosis of mammograms.

REPORTABLE OUTCOMES

Manuscripts, abstracts, articles, presentations:

J. Sklansky, Eric Y. Tao, M. Bazargan, C.J. Ornes, R.C. Murchison, S. Teklehaimanot, "Computer-Aided, Case-Based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications," *Academic Radiology*, Vol. 7, No. 6, June 2000, pp. 395-405.

Y. Price, J. Sklansky, E.Y. Tao, C.J. Ornes, M. Bazargan, S. Teklehaimanot, "Mapped Database for Case-Based Diagnosis in Digital Mammography," Scientific Exhibit on Breast Imaging at 1999 Annual Meeting of the Radiological Society of North America., *Radiology*, Vol. 213(P), November 1999, page 505.

J. Sklansky, E. Y. Tao, C. Ornes, A. C. Disher, "A Visualized Mammographic Database in Computer-Aided Diagnosis," *Computer-Aided Diagnosis in Medical Imaging,* edited by K. Doi, H. McMahon, M. L. Giger, K.R. Hoffmann, Elsevier, Amsterdam, 1999, pp. 215-220.

Jack Sklansky, EngScD, Chester J. Ornes, MS, "Database-Aided Diagnosis in Digital Mammography," *info*RAD Exhibit, 2000 Annual Meeting of the Radiological Society of North America, November 2000 (in preparation).

Funding based on work supported by this project:

"Database-Aided Telemammography," grant of $100,000 from California Telehealth and Telemedicine Center, for the period April 1, 2000 to March 31, 2002. Project Director: Jack Sklansky, EngScD.

Employment or research opportunities applied for and/or received on experiences/training supported by this award:

Farnoosh Nooryanni, MD, received and accepted an offer of a residency in Radiology at the University of Southern California with the help of her experience as a Radiology Fellow on our project. This appointment will begin in July 2001.

Yvette Price, MD, received and accepted an appointment as a Radiology Fellow at the UCLA Iris Cantor Center for Breast Imaging, beginning in July 2001. Dr. Price was a Radiology Resident and participated in our project's research at the time that she applied for this Fellowship.

CONCLUSIONS

Our diagnostic system shows promise of several important advances in the field of computer-aided diagnosis (CAD). One of these advances is the automation of the selection of groups of image features that are good discriminators between malignant and benign lesions. Another advance is the demonstration in our recent study (Appendix 2) that a properly designed interface between a human reader and a proved database of mammographic images may enable less experienced readers to exceed the performances of unaided, highly skilled readers – without the need for time-consuming training oon feature extraction.

Our design of a platform-independent architecture for multisatellite remotely sited diagnosis of mammograms shows promise of accelerating the development and growth of multi-satellite teleradiology, because it permits the use of low-cost PC computers in conjunction with state-of-the-art high-resolution radiological monitors.

REFERENCES

1. J. Sklansky, Eric Y. Tao, M. Bazargan, C.J. Ornes, R.C. Murchison, S. Teklehaimanot, "Computer-Aided, Case-Based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications," *Academic Radiology*, Vol. 7, No. 6, June 2000, pp. 395-405.

2. Y. Price, J. Sklansky, E.Y. Tao, C.J. Ornes, M. Bazargan, S. Teklehaimanot, "Mapped Database for Case-Based Diagnosis in Digital Mammography," Scientific Exhibit on Breast Imaging at 1999 Annual Meeting of the Radiological Society of North America., *Radiology*, Vol. 213(P), November 1999, page 505.

3. J. Sklansky, E. Y. Tao, C. Ornes, A. C. Disher, "A Visualized Mammographic Database in Computer-Aided Diagnosis," *Computer-Aided Diagnosis in Medical Imaging*, edited by K. Doi, H. McMahon, M. L. Giger, K.R. Hoffmann, Elsevier, Amsterdam, 1999, pp. 215-220.

APPENDICES

Appendix 1. Mammography Report Form

Appendix 2. Reprint of article: J. Sklansky, Eric Y. Tao, M. Bazargan, C.J. Ornes, R.C. Murchison, S. Teklehaimanot, "Computer-Aided, Case-Based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications," *Academic Radiology*, Vol. 7, No. 6, June 2000, pp. 395-405.

Appendix 3. Curriculum Vitae of Jack Sklansky, Eng.ScD

Appendix I

Mammography Report

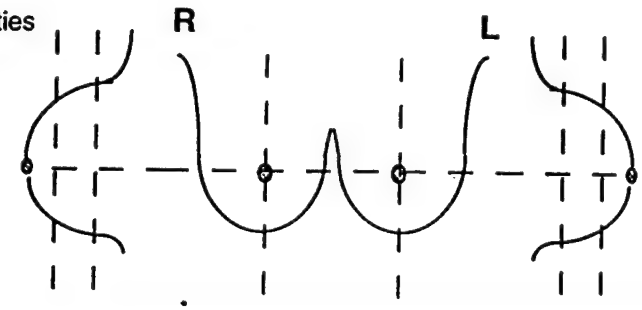
ent Study Identification Number _____ Age _____ Date _____

Screening Assessment Oa Ou Oo 1 2 3 4 5 Date _____
Final Assessment 1 2 3 4a 4b 4c 5 Date _____
Breast Composition 1 2 3 4
Clinical Correlation Finding correlates to clincial exam finding in ☐L ☐R ☐B breast(s) at _____ o'clo

Assessment Categories
0a = Additional films
0u = Ultrasound
0o = Outside Films
1 = Negative
2 = Benign finding
3 = Probably benign
4 = Suspicious abnormality (a-mild, b-moderate, c-high)
5 = Highly suggestive of malignancy

Breast Composition
1 = Almost entirely fat
2 = Scattered fibroglandular densities
3 = Heterogeneously dense
4 = Extremely dense

Mammography Findings



MASS

Size /Number	In area of density?	Shape	Margins	Density
___ cm ___#	☐ Yes ☐ No	☐ Round ☐ Oval ☐ Lobular ☐ Irregular	☐ Circumscribed ☐ Ill-defined ☐ Microlobulated ☐ Spiculated ☐ Obscured	☐ High ☐ Equal ☐ Low ☐ Fat containing
___ cm ___#	☐ Yes ☐ No	☐ Round ☐ Oval ☐ Lobular ☐ Irregular	☐ Circumscribed ☐ Ill-defined ☐ Microlobulated ☐ Spiculated ☐ Obscured	☐ High ☐ Equal ☐ Low ☐ Fat containing

CALCIFICATIONS

Distribution Modifiers
☐ Grouped/Clustered
☐ Linear
☐ Segmental
☐ Regional
☐ Diffuse/Scattered

Typically Benign
☐ Skin
☐ Vascular
☐ Coarse
☐ Large rod-like
☐ Round
☐ Lucent-centered
☐ Eggshell/Rim
☐ Milk of Calcium
☐ Suture
☐ Dystrophic
☐ Punctate

Intermediate Concern
☐ Amorphous or Indistinct

Higher Probability of Malignancy
☐ Pleomorphic/hetereogenous
☐ Fine, linear branching

Other Findings
☐ Skin thickening
☐ Trabecular thickening
☐ Skin lesion
☐ Skin retraction
☐ Nipple retraction
☐ Axillary adenopathy
☐ Asymmetric breast tissue
☐ Focal asymmetric density
☐ Architectural distortion

Pathology Diagnosis: Benign _____ Malignant _____

Comments:

_____

_____ _____

PATHOLOGY CODES

PATHOLOGY - MALIGNANT

.NC Metastatic disease Axillary Node
:C C olloid (mucinous) C arcinoma
:I C omedocarcinoma (I ntraductal)
:P ntra C ystic P apilloma
)S uctal carcinoma in-S itu DCIS
C I ntracystic papillary C arcinoma
D I nvasive D uctal carcinoma
I) I nvasive and I n-situ cancer
L I nvasive L obular carcinoma
N IN flammatory carcinoma
P P apillary I nvasive carcinoma
.N L ymph N ode
.Y LY mphoma
fB M etastatic lesion to the B reast
fC M edullary C arcinoma
fI M ultifocal I ntraductal carcinoma
C P apillary C arcinoma in-situ
D P aget's D isease
.M R ecurrent M alignancy
S arcoma
C T ubular C arcinoma
THER:_____

PATHOLOGY - HIGH RISK LESIONS

TD AT ypical D uctal hyperplasia
TL AT ypical L obular hyperplasia
S obular Carcinoma in S itu
P P eripheral duct P apilloma

'alse negatives only:

PATHOLOGY - BENIGN

AB AB scess
AD AD enosis
ANL A xillary N ode with L ymphoma
BC B enign C yst
DE D uct E ctasia
DH D uctal H yperplasia
EC E pidermal Inclusion C yst
FA F ibroA denoma
FB F oreign B ody
FC F ibroC ystic
FF F ocal F ibrosis
FN F at N ecrosis
GA GA lactocele
GF G iant F ibroadenoma
GYN GYN ecomastia
HB H amartoma of the B reast
HE HE matoma
IM I ntra M ammary node
LB L ipoma of the B reast
LH L obular H yperplasia
LN L ymph N ode
LP L arge duct P apilloma
NA N o A bnormality
PT P hylloides T umor
RS R adial S car
SA S clerosing A denosis
SE SE roma
SG S ilicone G ranuloma
ST S car Tissue
OTHER: _____

Computer-aided, Case-based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications[1]

Jack Sklansky, EngScD, Eric Y. Tao, PhD, Mohsen Bazargan, PhD
Chester J. Ornes, MS, Robert C. Murchison, MD, Senait Teklehaimanot, MPH

Rationale and Objectives. The purpose of this study was to evaluate the effectiveness of a mapped-database diagnostic system in reducing the incidence of benign biopsies and misdiagnosed cancers among mammographic regions of interest (ROIs).

Materials and Methods. A novel neural network was devised (*a*) to respond to a query ROI by recommending to biopsy or not to biopsy and (*b*) to map each ROI in the database as a dot on a computer screen. The network was designed so that clusters in the array of dots help the radiologist to find proved ROIs visually similar to the query ROI. This mapped-database diagnostic system was restricted to ROIs with visible microcalcifications. The neural network was trained with a stored database of 80 biopsy-proved ROIs.

Results. Four radiologists acting independently on 100 ROIs recommended biopsies for 18, 15, 28, and 18 benign ROIs and misdiagnosed cancers in 11, 12, 7, and eight ROIs, respectively. Interaction with the mapped-database system reduced the numbers of benign biopsies to 11, eight, 18, and 10 cases and of misdiagnosed cancers to eight, seven, four, and three cases, respectively. Statistical analysis indicated that three radiologists achieved significant improvements at $P \leq .02$ and the fourth achieved a substantial improvement at $P \leq .07$.

Conclusion. By using a mapped database of proved mammographic ROIs containing microcalcifications, radiologists may statistically significantly reduce the numbers of benign biopsies and misdiagnosed cancers.

Key Words. Computer-aided diagnosis; digital mammography; microcalcifications.

A critical aspect of mammographic diagnosis is deciding whether to recommend biopsy. Approximately two benign lesions are sampled for biopsy for every malignant lesion detected (1). In a recent study of 2,400 women undergoing mammographic screening during a 10-year period (2), an additional $33 was spent on evaluating false-positive results for every $100 spent on screening. Among the women in that study, the cumulative risk of a false-positive result after 10 mammograms was 49.1%. Thus, it would be highly desirable to reduce the frequency of benign biopsies during mammographic screening without increasing the number of missed cancers.

The objective of this study was to evaluate the effectiveness of a recently devised "mapped-database diagnostic system" in reducing the frequency of benign biopsies and misdiagnosed cancers among mammographic regions of interest (ROIs). The principal difference between this system and earlier computer-aided diagnostic systems for mammography is the facilitation of diagnostic reasoning by a database of proved ROIs. In this study, the presented mammographic images and stored database are restricted to ROIs, and the ROIs themselves are restricted to those revealing apparent microcalcifications.

Interpretation of mammograms consists of two major components: *detection* and *diagnosis*. In detection, the

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radiologist typically examines four full-field views—two views of each breast. In these views, the radiologist may detect one or more ROIs revealing possible lesions. In diagnosis, the radiologist analyzes one or more ROIs to determine whether biopsy should be performed or whether the patient should be recalled for further examination. Thus, analysis of ROIs is an important part of clinical mammography, particularly in establishing a diagnosis. This study focused on the ability of the mapped-database diagnostic system to reduce the number of negative biopsy results and of misdiagnosed cancers associated with the analysis of ROIs.

By restricting the images used in this study to ROIs, thereby excluding the full-breast views, we reduced much of the cost and duration of the experiments, but at the expense of eliminating contextual evidence. A further reduction in cost—and in diagnostic accuracy—was obtained by replacing film mammograms with digital images displayed with a cathode ray tube monitor (3). By anticipating the widespread growth of digital mammography while recognizing these reductions in diagnostic accuracy, this relatively inexpensive study examined the effect of the mapped-database system on diagnostic accuracy during digital mammography.

In the mapped-database system, an artificial neural network responds to a mammographic ROI by recommending, or not recommending, biopsy. In addition, the neural network maps a database of ROIs from proved mammograms onto a two-dimensional display as an aid to establishing a diagnosis. The network does this by mapping each ROI into a dot on a screen and arranging these dots so that they cluster into radiographically similar subclasses. We refer to this representation as a *mapped database*. In addition to producing the mapped database, the neural network partitions the screen into two decision regions: one for a biopsy being recommended, and the other for a biopsy not being recommended. We call the resulting display a *relational map* (4). By annexing this neural network to a means of quickly retrieving and viewing ROIs that are mapped close to the query, the radiologist is given a simple way of conversing with the database to enhance the reliability of the diagnostic decision. Thus, this system amplifies the radiologist's powers of "case-based reasoning" (5) and acts somewhat like a second reader with consensus (6).

This concept led to construction of a mammographic diagnostic system built on the basis of several earlier developments: (*a*) algorithms for detecting and analyzing clusters of microcalcifications (7–10), (*b*) large databases of digitized mammograms (11–15), (*c*) genetic algorithms for high-speed parallel search (16), and (*d*) "visual neural classifiers" (ie, specialized neural networks) that map multidimensional features and multidimensional decision surfaces onto two-dimensional displays (4). We refer to this as a *mapped-database diagnostic system*. The test results reported herein suggest that for mammograms with detectable microcalcifications, this system can provide a new level of reliability for mammographic diagnosis.

The most pertinent earlier work regarding database-aided mammographic diagnosis is that by Swett and his colleagues at Yale University (17). Their mammographic database system, MAMMO/ICON, required a verbal medical history and verbal mammographic descriptors to supplement each mammogram. This system could provide diagnostic advice that depended on semantic similarities of the verbal descriptors and medical histories (18). A shortcoming of this technology, however, was its dependence on verbal descriptors to match information that was essentially pictorial and nonverbal. Among radiologists, there may be considerable variability in the specific words used to describe the pertinent properties of any given mammogram. This variability may impair the reliability of retrieving similar mammograms filed according to verbal descriptors. Another shortcoming was the manual construction of the verbal descriptors for the mammograms, in contrast to the possibility of automatic extraction and counting of key words in text.

Among other published articles on computer-aided diagnosis of mammograms, those by Getty et al (19), Jiang et al (9), and Chan et al (20) are particularly relevant to the present work. Getty et al (19) demonstrated that a checklist of descriptors (ie, "features") combined with a digital classifier could be an effective aid in establishing the diagnosis during mammography. These features, as in our experiment, were for the most part descriptors of a "focused abnormality" (ie, the equivalent of ROI as used here). The protocol for aiding the radiologist included a computer-alone reading, which was followed with a second reading by the radiologist (analogous to a double reading with consensus). A second contribution by Getty et al was the demonstration that a carefully selected set of features, when coupled with a session to train radiologists to estimate these features, could enable computer-aided generalists to read film mammograms almost as well as highly skilled specialists. Jiang et al (9) demonstrated the potential of automatically extracting features from microcalcifications, coupled with an artificial neural network, for computer-aided diagnosis. The methods in both of these studies (9,19), however, still required substantial human involvement in the computer-aided procedure. In the method of Getty et al (19), each radiologist estimated the numeric level of intensity or level of confidence for the existence of each feature; in the method of Jiang et al (9), the location of each microcalcification was determined manually. This

amount of human involvement likely makes these techniques impractical for clinical use.

Chan et al (20) restricted human involvement to identifying in each view an ROI enclosing a mass. This level of human involvement is likely to be practical during clinical applications, because finding ROIs is part of the usual procedure for interpreting mammograms. As in the method of Getty et al (19), the radiologist-reader in the method of Chan et al (20) was asked to make a final estimate regarding the likelihood of malignancy in a presented mammogram after first performing an unaided estimation and then receiving the computer's estimate. In that study, the performance of the computer alone was comparable to that of the best performing unaided radiologist-reader and to the performance of six aided radiologist-readers as a group.

MATERIALS AND METHODS

A retrospective study of the mapped-database system was performed during June 1998. The ROIs included in this study were restricted to those exhibiting microcalcifications. For this study, we acquired a database of 200 ROIs from 138 proved cases. Biopsy results were included with each ROI. Four radiologists from the clinical faculty of the Department of Radiology at King/Drew Medical Center (KDMC) read the digitized images in this study. None of these radiologists was familiar with the cases, and all of them were certified for mammography by the U.S. Food and Drug Administration. Their postresidency experience in reading mammograms was 29 years, 10 years, 5 years, and 6 months; these readers are referred to as R_1, R_2, R_3, and R_4, respectively.

The ROIs in the database were excised from digitizations of film mammograms provided by KDMC and by the University of California at Los Angeles (UCLA) Iris Cantor Center for Breast Imaging. In all cases associated with these mammograms, either biopsy or follow-up with subsequent mammography was performed. From these mammograms, all 138 cases that revealed microcalcifications were selected for this study. Fifty-two cases were from KDMC, and 86 were from UCLA. The selected mammograms were digitized at KDMC on a scanner-digitizer (Lumiscan 85; Lumisys, Sunnyvale, Calif) at a pixel width of 50 μm and a pixel depth of 12 μm.

For each film mammogram, the location of an abnormality containing a cluster of microcalcifications was provided in the medical record that accompanied the image. From this information, we constructed a 512 × 512-pixel ROI enclosing each designated cluster of microcalcifications. This construction yielded 160 ROIs. No two ROIs in this set were views of the same lesion. To each ROI we applied an automatic microcalcification detector and segmenter that was developed during an earlier study (7). An additional 40 normal ROIs were also added to this database, thereby making a total of 200 ROIs in this study. These normal ROIs were included to ensure that readers would have the impression that not all ROIs in the set used to test the system (described later) were abnormal. The normal ROIs were obtained from cases involving patients who did not undergo biopsy and were not recalled during a period of at least 18 months. Within each of these cases, the normal ROI was selected arbitrarily.

Of the abnormal ROIs (ie, those containing microcalcifications), 64 were proved at biopsy to be benign, 49 were proved at biopsy to be malignant, and 47 were proved at follow-up to be benign (ie, both the ROI and the follow-up findings did not produce a recommendation for biopsy). At least 18 months elapsed between two successive examinations, and none of the radiologists on our reading panel had seen these ROIs before this study. One radiologist (R_1) partitioned the 200 ROIs into groups such that ROIs in the same group were visually similar. We refer to these groups as *perceptual groups*. No restriction was placed on the number of perceptual groups, although the radiologist (R_1) was informed that eight groups were formed by another radiologist during another set of ROIs in an earlier experiment (21). The radiologist (R_1) partitioned the 200 ROIs into the following 12 groups: (*a*) amorphous with mass, (*b*) lobular and ductal, (*c*) amorphous, (*d*) pleomorphic and scattered, (*e*) lobular, (*f*) granular, (*g*) casting, (*h*) punctate scattered, (*i*) linear ductal, (*j*) vesicular, (*k*) oil cyst, and (*l*) no visible abnormality.

Computer-aided reading of the test set by the reading panel was performed more than a month after partitioning of the ROIs into perceptual groups. The intent of this 1-month delay was to suppress the memory of the 200 ROIs in the radiologist who partitioned them into the perceptual groups.

The database was then divided into two sets, D and T, each of which consisted of 100 ROIs. D was used for the design of the diagnostic system, and T was used for testing of the system. The 160 abnormal ROIs were randomly partitioned several times into two equal parts, D_A and T_A, until a (D_A, T_A) pair was found such that D_A and T_A each contained at least two ROIs from each perceptual group. (Ensuring representation of at least two ROIs from each perceptual group, however, may have biased the diagnostic system somewhat in favor of the neural network. On the other hand, not achieving this representation would have biased the study against the neural network.) D_A consisted of 54 benign and 26 malignant ROIs. T_A consisted of 57 benign and 23 malignant ROIs. Because no two ROIs were images of the same lesion, all lesions in T

Table 1
Features Extracted from Microcalcifications and Regions of Interest

Feature	Symbol	Formula	Clinical Importance
Area	*A*	Number of pixels in the calcification labeled ≥ 0	Large calcification may suggest a benign abnormality.
Perimeter	*P*	Number of pixels in central boundary (label = 0)	Large calcification may suggest a benign abnormality.
Irregularity	*I*	A/P^2	Irregular boundary may suggest a malignant abnormality.
Mean intensity	*MI*	Average brightness of pixels labeled ≥ 0	Bright calcification may suggest a benign abnormality.
Standard deviation of intensity	*SI*	Standard deviation of pixels labeled ≥ 0	Large *SI* may suggest an irregular density and malignancy.
Mean of exterior intensity	*ME*	Average brightness of pixels within 5 pixels from the calcification	Large *ME* may suggest a dense and malignant tissue.
Standard deviation of exterior intensity	*SE*	Standard deviation of pixels within 5 pixels from the calcification	Large *SE* may suggest a malignant tissue.
Contrast	*C*	$\|MI - SI\| - MI$	Large contrast may suggest a benign abnormality.
Sharpness of boundary	*SH*	Average change in brightness between pixels labeled 0 or 1 and those labeled −1 or −2	Large *SH* may suggest a benign abnormality.
Inner shell contrast	B_1	Average change in brightness between pixels labeled 2 and those labeled 1	Large B_1 may suggest a benign abnormality.
Center shell contrast	B_0	Average change in brightness between pixels labeled 1 and those labeled 0	Large B_0 may suggest a benign abnormality.
Outer shell contrast	B_{-1}	Average change in brightness between pixels labeled 0 and those labeled −1	Large B_{-1} may suggest a benign abnormality.
Exterior shell contrast	B_{-2}	Average change in brightness between pixels labeled −1 and those labeled −2	Large B_{-2} may suggest a benign abnormality.
Concavity index	*CI*	Area of region between the calcification and its convex hull	Large *CI* may suggest a malignancy.
Shape signature	*SG*	$\left[\int \lvert r(\theta) - R \rvert d\theta\right] / R$, where *r* is radial distance of boundary from centroid, *R* is the mean of *r*, and θ is orientation of *r*	A large *SG* may suggest benign tissue.
Aspect ratio	*R*	Ratio of maximum central diameter to minimum central diameter	Large *R* may suggest a malignancy.
Count	*N*	Number of calcifications	Large count may suggest malignancy.
Structural index	*S*	$1 - d\sqrt{(N/AC)}$, where *d* is the average distance of the closest calcification and *AC* is area spanned by cluster	Large *S* indicates nonuniform distribution of microcalcifications and, hence, may suggest malignancy.

were distinct from all lesions in D. The 40 normal ROIs were partitioned several times into two equal parts, D_N and T_N, until a (D_N, T_N) pair was found such that D_N and T_N had similar distributions in the mapped feature space. The final design set D was the union of D_A and D_N. The final test set T was the union of T_A and T_N. These procedures were performed to ensure the design set was representative of the types of abnormalities occurring in the test set. As mentioned, the normal ROIs were included to ensure the readers would have the impression that not all ROIs in T were abnormal. Because diagnostic (rather

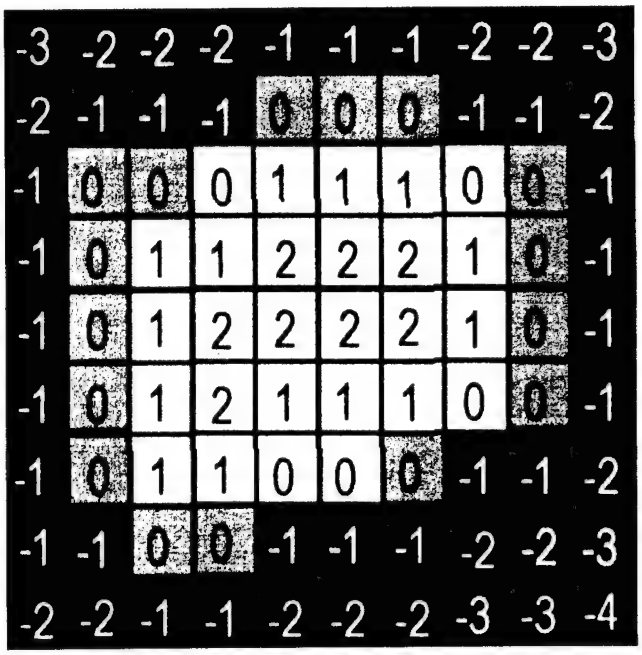

Figure 1. Numeric labeling for the pixels of a digital model representing a typical microcalcification. The label of each pixel is the number of pixel displacements of that pixel from the medial axis of the boundary of the microcalcification. Thus, 0 denotes a pixel on the medial axis of the boundary, 1 a pixel just inside the boundary, –1 a pixel just outside the boundary, and –2 a pixel just outside the –1 region.

than detection) efficacy was paramount in this study, the mapped-database system in this study was designed to analyze only the abnormal ROIs. Consequently, readings of the normal ROIs were not included in our calculations of specificity, sensitivity, and other measures of performance.

From each abnormal ROI, 18 candidate features were extracted. Each candidate feature was designed to reflect one or more properties of calcifications (or groups of calcifications) that are meaningful to the radiologist. These features were based on the American College of Radiology's Breast Imaging Recording and Data System (BI-RADS) descriptors for interpreting mammograms, the book by Lanyi (22), and discussions with the radiologists on our panel. Unfortunately, most BI-RADS descriptors are too subjective for encoding into computer-executable formulas. Consequently, the features we extracted were inspired by, but not necessarily a direct implementation of, the BI-RADS descriptors. A formulation and brief clinical justification for each of these features are given in Table 1. In the first two columns of this table, a name and a mathematical symbol denote each feature. A formula for each feature is given in the third column. The fourth column contains a brief description of the clinical importance of the feature. Some of the formulas refer to numerical pixel labels –2, –1, 0, and 1. The label on each pixel P is the number of pixel displacements of P from the boundary of a calcification. The label 0 denotes a pixel on the boundary, 1 denotes a pixel just inside the boundary, –1 denotes a pixel just outside the boundary, and –2 denotes a pixel just outside the –1 region. These labels are illustrated in Figure 1, which shows a digital model of a typical microcalcification.

Starting from this set of candidate features, a genetic algorithm searched for those subsets of features that were most effective in discriminating malignant from benign cases in the database. This algorithm was designed in accordance with the genetic feature selector described by Siedlecki and Sklansky (23). In this algorithm, each candidate subset is represented by a binary string (ie, a sequence of 0s and 1s). The value (0 or 1) of the nth element of the string indicates whether the nth feature belongs to the candidate subset. We refer to this string as a *chromosome*. A population of 100 chromosomes was transformed by an evolutionary process consisting of mutation, mating, and reproduction to form a sequence of new populations or "generations" under the guidance of a penalty function that accounted for the k-nearest-neighbor discriminability of the feature vectors in each feature subset and for the number of features in the subset. The sizes of the new populations were kept constant at 100. This evolutionary process also optimized the value of k. To ensure an acceptably low rate of misdiagnosed cancers, the penalty function gave seven times as much weight to misdiagnosing a cancer as to recommending a biopsy that was benign. (The weight was chosen empirically so that the nearest-neighbor classifier would produce only one or two missed cancers on the data set.) This algorithm selected the following four features: (*a*) mean area, (*b*) mean aspect ratio, (*c*) mean irregularity (ie, noncircularity), and (*d*) number of microcalcifications. Another algorithm extracted these four features from each ROI, thus forming a four-dimensional *feature vector* as a descriptor of that ROI.

A five-layer neural network was constructed in accordance with the architecture and the design principles described by Ornes and Sklansky (24). Each node in this architecture represented an artificial neuron that consisted of a weighted summation followed by a sigmoidal activation function. The first layer consisted of four input neurons, one for each selected feature. The second and third layers consisted of three and two neurons, respectively, to reduce the dimensionality of feature space. The two-neuron layer produced x and y coordinates (one from each of the two neurons) to represent each ROI as a dot on a relational map. For each ROI in the design set, this dot was labeled to indicate whether the biopsy was benign or malignant. The two

neurons in the fifth layer classified each feature vector as either "biopsy recommended" or "biopsy not recommended." (The neuron producing the larger of the two outputs determined the class of the feature vector.) By entering every permissible pair of map coordinates at the input to the fourth layer, the fifth layer thus produced a relational map in which all pixels were labeled as either biopsy recommended or biopsy not recommended.

Using the four features selected by the genetic algorithm, the neural network was trained by backpropagation (ie, a form of gradient descent in the space formed by the weights at the inputs to the neurons) on the design set D_A, thereby producing the trained neural network NN(D_A) (4). In accordance with our design philosophy for this study, the neural network was trained only on abnormal ROIs. The biopsy outcomes (ie, benign and malignant) in the database were the desired output classes in the trained neural network, which produced a two-dimensional map of D_A and a near-optimal partition of this map into two decision regions. These decision regions were associated with the decisions of biopsy recommended and biopsy not recommended. The training was stopped when the mean square error converged to a nearly constant value. This design strategy, and the relatively low error rate of the neural network on the test set T, encouraged us to believe that the network was then adequately trained.

The boundary separating the decision regions is referred to as a *decision curve*. The decision curve is substantially smoother than the variability of the data, which is the result of the averaging produced by the backpropagation training and the small number of neurons compared with the number of feature vectors in the training set. The neural network tends to produce decision regions that are responsive to statistical models of the training data rather than to the training data itself. Specifically, the training algorithm minimized a weighted sum-of-squared-error function, which yielded outputs that were estimates of Bayesian posterior probabilities that the input vector belonged to the corresponding class (ie, biopsy recommended or biopsy not recommended). Thus, the decision curve produced by the neural network tends to "generalize" the training data and, thereby, to make good decisions on future data not included in the training set (25).

The trained neural network displayed the query and the ROIs in D_A as dots, with each dot being located by the x and y coordinates produced by the two neurons (one coordinate from each neuron) at the two-neuron layer of the network. We refer to the space spanned by x and y as the *mapped feature space* and to the map of D_A as a *mapped database*. The map of D_A and its decision regions are depicted in Figure 2. We call this a *relational map*. Here, the black region represents biopsy recommended, and the white region represents biopsy not recommended. The decision curve is the boundary between the black and the white regions. The symbols O and X denote benign and malignant feature vectors, respectively. The symbol ■ denotes a query.

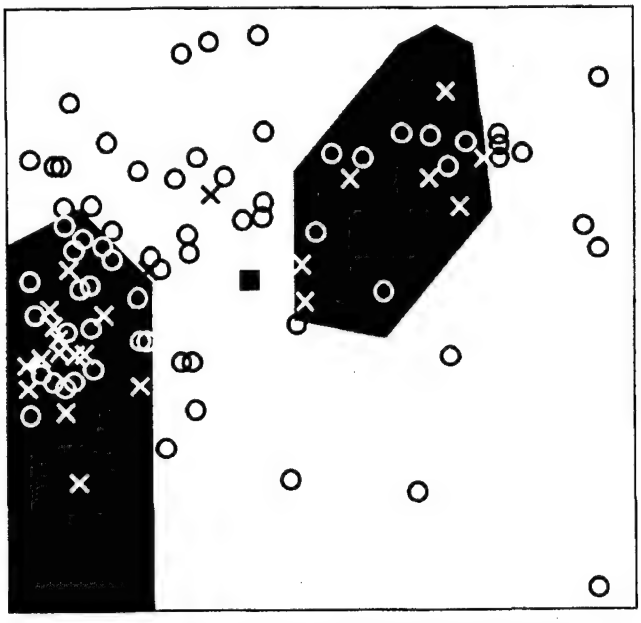

Figure 2. Relational map of design set *D* and the query ROI. Each malignant case is labeled X, and each benign case is labeled O. The query ROI is labeled ■.

A weakness of the mapped-database system is that it does not reveal the quantitative relationships between the mapped feature space and the unmapped features. This weakness is compensated for, however, by the ability of the relational map to cluster visually and diagnostically similar ROIs and by the map's representation of a multidimensional decision surface as a decision curve (or as several disjoint decision curves) in the mapped feature space. The clustering helps the radiologist to find ROIs that are visually similar to the query, and the decision curve helps the radiologist to determine the confidence of the neural network in its recommendations either for or against performing biopsy. Further insight into the relationships between the mapped feature space and the original features can be obtained by making available the numerical values of the original features of each mapped ROI to the radiologist-user.

The user interface presented on the computer monitor is illustrated in Figure 3. This interface guides the radiologist-user through the steps of diagnosis. Identification numbers in this figure (eg, 011318) were constructed so that patients could not be identified from the information in the figure. The mammographic image in the upper left is an enlargement of the ROI

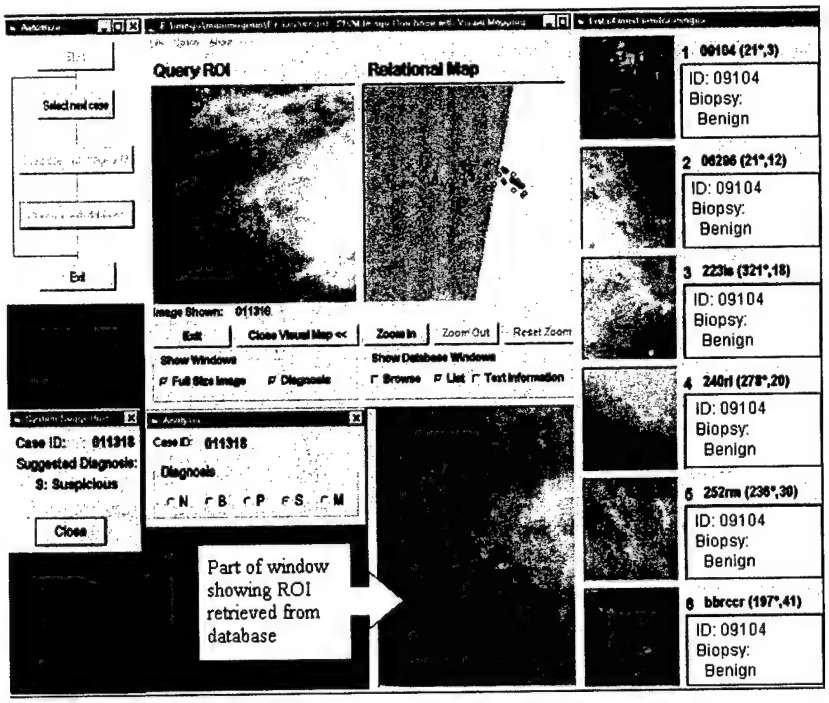

Figure 3. User interface for mammographic diagnosis.

of a query mammogram. Digital magnification and negative-to-positive inversion were provided as options on the user interface. In response to a prompt from the interface, the radiologist first determines an "unaided" diagnosis of this ROI and reports it in the BI-RADS code (26) by clicking N, B, P, S, or M, which denote normal, benign, probably benign, suspicious (possibly malignant), and almost definitely malignant, respectively. In this study, we assumed that N, B, and P corresponded to biopsy not recommended and that S and M corresponded to biopsy recommended. This assumption conformed to the clinical practice at KDMC. We instructed each reader to produce the unaided diagnosis as if it were the final diagnosis for the examination. No time limit was imposed on this diagnosis.

In this study, the diagnostic process began by establishing an unaided diagnosis, which was followed immediately by establishing an aided diagnosis (analogous to double reading). We assumed that the operating point (ie, the subjective decision threshold for a BI-RADS symbol) of the unaided radiologist might be affected by that radiologist's anticipation of an aided diagnosis, but that the receiver operating characteristic (ROC) of the unaided diagnosis was unaffected by that anticipation.

Immediately after the unaided diagnosis was established, the relational map was presented to the radiologist. This map contained the mapped database, mapped query, and distinctively colored decision regions. Thumbnail images of six ROIs near the query in the mapped feature space were presented at the right of the monitor screen. From these images, the radiologist retrieved for review those with a visual appearance that seemed to be most similar to that of the query. This review was facilitated by an enlarged view of the retrieved ROI and the accompanying biopsy reports. On the basis of this interaction, the radiologist selected a BI-RADS score for the ROI. Again, the reader was not restricted by a time limit for establishing this diagnosis, and both magnification and inversion were provided as options on the user interface.

To evaluate the diagnostic improvement provided by the mapped-database diagnostic system, we computed the ROC of each unaided radiologist, of each computer-aided radiologist, and of the computer alone. Each ROC accounted for the BI-RADS responses of the radiologists and for the outcomes of the biopsies. The diagnostic performance of each radiologist was measured by the area A_z under the ROC curve, which is an estimate of the probability for a correct decision in a forced choice between two ROIs, one of which is malignant and the other of which is benign (27). Thus, A_z must lie between a minimum of 0.5 (corresponding to an unbiased random guess) and a maximum of 1 (perfect performance).

We also computed the average performance of the four radiologists when unaided by the mapped-database system and when aided by the mapped-database system. LABMRMC (C.E. Metz, LABMRMC 1.0B, beta version 3, University of

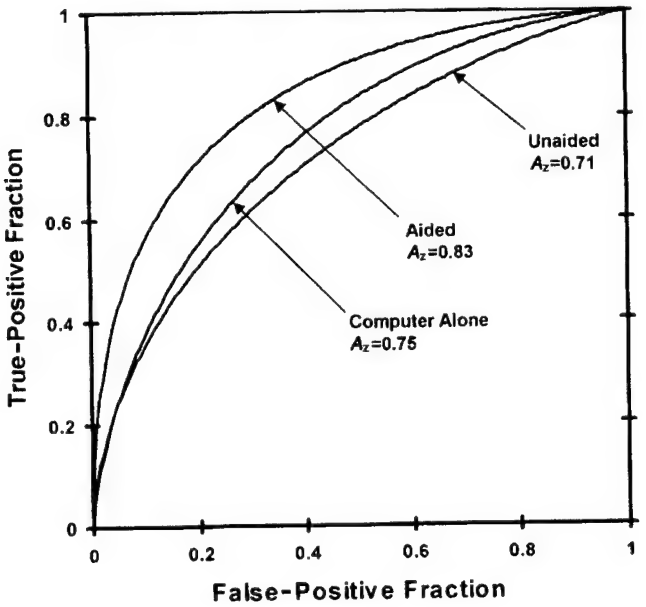

Figure 4. ROC curves for radiologist R_1 and for the computer alone.

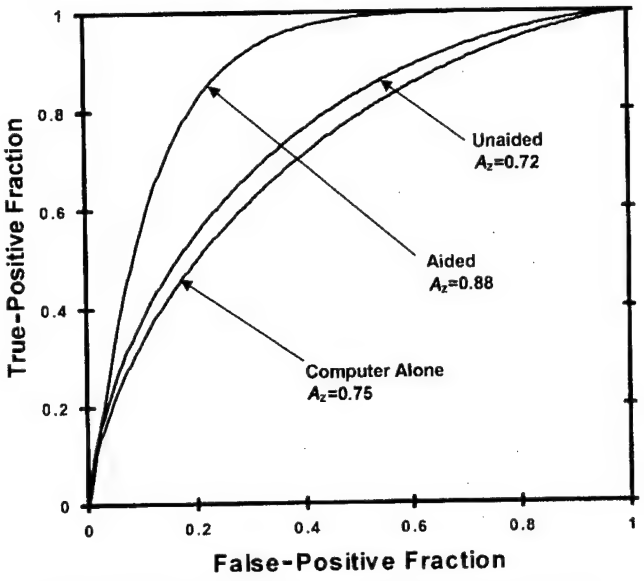

Figure 5. ROC curves for radiologist R_2 and for the computer alone.

Chicago, Chicago, Ill) (28) was employed to calculate the maximum likelihood estimates for the parameters of binormal models and the statistical significance of the change in areas under the ROC curves for the unaided and the aided reading modalities. The ROC curves representing the average performance of the unaided radiologists were computed by averaging their estimated slopes and intercepts in normal deviate space. This same process was also performed for the aided radiologists.

The mapped-database diagnostic system was designed and implemented at the University of California, Irvine, on an IBM-PC–compatible computer with a 66-MHz Intel 486 processor, 32 MB of random access memory, and a 17-inch CTX monitor with 1,280 × 1,024 pixels running on a Microsoft (Redmond, Wash) Windows 95 operating system. The software development environment was Microsoft Visual C++ 4.0 for image-processing functions and Microsoft Visual Basic 5.0 for the user interface. Testing of this system was performed at KDMC on another IBM-PC–compatible computer with a 233-MHz Pentium II processor, 64 MB of random access memory, and a 17-inch monitor (Vivitron; Gateway 2000, Sioux City, SD) with 1,280 × 1,024 pixels running on a Microsoft Windows 95 operating system.

RESULTS

The ROC curves, labeled by their A_z values, are shown in Figures 4–8. The statistical significance of the changes

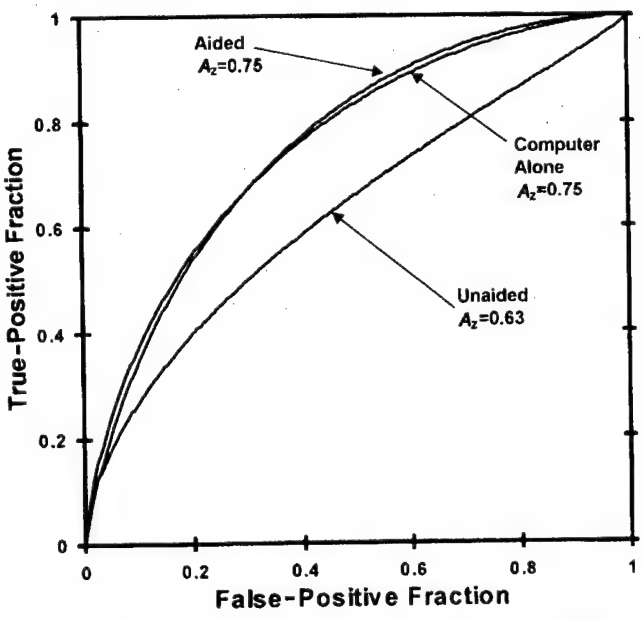

Figure 6. ROC curves for radiologist R_3 and for the computer alone.

in these A_z values is reported in Table 2. The columns of A_z values for the unaided radiologist, the aided radiologist, and the computer alone are labeled A, B, and C, respectively. The column labeled A-B denotes the values of P associated with the increase in A_z obtained by replacing an unaided radiologist with the corresponding aided radiologist. The values of P listed in Table 2 are two-tailed and

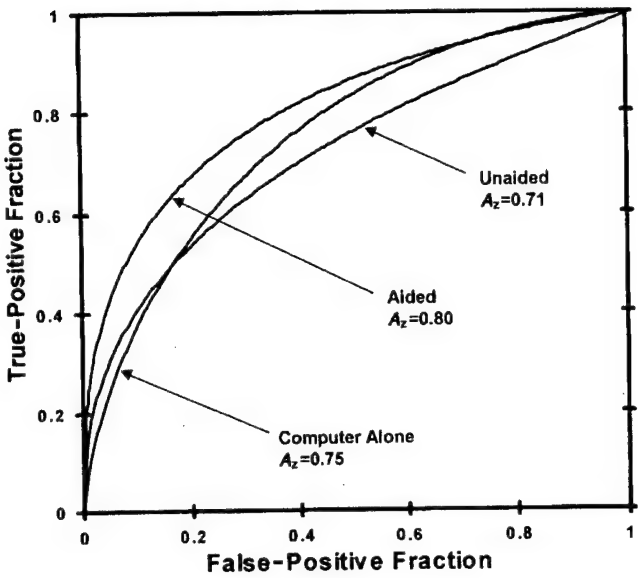

Figure 7. ROC curves for radiologist R_4 and for the computer alone.

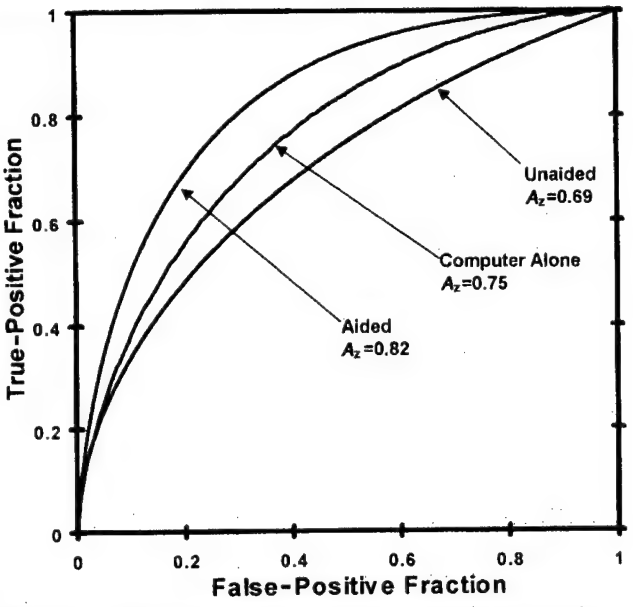

Figure 8. ROC curves for the average performance of the four radiologists.

Table 2
Comparison of ROC Curves for the Unaided Radiologist, the Aided Radiologist, and the Computer Alone

	A_z			P
Reader	A, Unaided	B, Aided	C, Computer Alone	A-B,Two-tailed
R_1	0.7150	0.8354	0.7533	0.0157
R_2	0.7179	0.8814	0.7533	0.0013
R_3	0.6277	0.7538	0.7533	0.0015
R_4	0.7157	0.8077	0.7533	0.0636

were calculated under the assumption that the distribution of each estimated change in A_z, divided by the estimated standard error of that change, arose from a normal distribution. These values of P were computed by using the ROCKIT software (C. E. Metz, ROCKFIT 0.9B, beta version, University of Chicago, Chicago, Ill, 1998).

The information in Figures 4–7 indicates that (*a*) every aided radiologist outperformed the same unaided radiologist, (*b*) no unaided radiologist outperformed the computer alone, and (*c*) three aided radiologists outperformed the computer alone and the fourth aided radiologist (R_3) performed approximately equal to the computer alone. The information in Table 2 indicates that the A_z values of the unaided radiologists ranged from 0.6277 to 0.7179, and that those of the aided radiologists ranged from 0.7538 to 0.8814. The size of the changes in A_z among the radiologists ranged from 0.0920 to 0.1635. Table 2 also indicates that the A-B changes in A_z (ie, unaided-to-aided changes in A_z) were statistically significant at $P < .002$ for radiologists R_2 and R_3, at $P < .02$ for radiologist R_1, and at $P < .07$ for radiologist R_4. After application of the Bonferroni correction for multiple comparisons, these three P bounds became .008, .08, and .28, respectively (29). Other changes in A_z—namely, A-C (ie, unaided–to–computer alone changes) and B-C (ie, aided–to–computer alone changes)—were not statistically significant.

Figure 8 shows the average performance of the four radiologists when unaided by the mapped-database system and when aided by the mapped-database system. Results of the LABMRMC analysis indicate that performance of the aided radiologists, as a group, was statistically superior to that of the unaided radiologists as a group ($P < .05$).

At KDMC, the diagnostic scores S and M are conventionally interpreted as being biopsy recommended, and N, B, and P are interpreted as being biopsy not recommended. In accordance with this convention, we calculated the numbers of negative biopsies and misdiagnosed cancers, as well as the sensitivities and specificities of each radiologist, both aided and unaided by the mapped-database system. These results are shown in Tables 3–5. Tables 3 and 4 show the numbers of recommended benign biopsies and misdiagnosed cancers. Table 5 shows the sensitivities and specificities. The mapped-database diagnostic system helped every radiologist reduce the number of benign biopsies by 40% or more while simultaneously reducing the number of misdiagnosed cancers. All

Table 3
Numbers of Recommended Benign Biopsies for the Unaided Radiologist and the Aided Radiologist

Reader	Unaided Radiologist	Aided Radiologist
R_1	18	11
R_2	15	8
R_3	28	18
R_4	18	10
NN	24	...

Note.—Number of ROIs from benign cases: 57. NN = neural network.

Table 4
Numbers of Misdiagnosed Cancers for the Unaided Radiologist and the Aided Radiologist

Reader	Unaided Radiologist	Aided Radiologist
R_1	11	8
R_2	12	7
R_3	7	4
R_4	8	3
NN	4	...

Note.—Number of ROIs from malignant cases: 23. NN = neural network.

the radiologists also increased both their sensitivities and specificities through their interaction with the mapped-database system. The statistical significances of these increases ranged from $P < .01$ to $P \leq .12$ on the basis of a comparison of proportions (30).

As mentioned, the sensitivities, specificities, and ROCs were calculated on the basis of the 160 abnormal ROIs and the responses of the panel of radiologists to them. The responses of the panel of radiologists to the 20 normal ROIs (the remaining 20 normal ROIs were in the set D_N) were excluded from these calculations, because in this study, the mapped-database diagnostic system was designed only to interpret abnormal ROIs.

DISCUSSION

Figures 4–8 and Tables 2–5 indicate that the diagnostic performances of the aided radiologists were statistically significantly improved compared with those of the unaided radiologists. Table 2 shows that the sizes of these improvements in A_z for the current study are comparable to those in A_z found during a recent study concerning computer-aided characterization of mammographic masses (20).

We are also encouraged by the improved performance of the aided radiologists over that of the computer alone, as indicated in Figures 4, 5, 7, and 8 and in Table 2, although the number of cases was insufficient to prove statistical significance of these improvements. Table 5 shows that the mapped-database diagnostic system enabled substantial increases in specificities and sensitivities for all the radiologists in our panel. We conclude that for ROIs containing microcalcifications, the mapped-database diagnostic system shows promise in helping most radiologists to raise their diagnostic performances substantially over their unaided performances while providing relevant images from a proved database to support the radiologists' aided diagnoses. In particular, these radiologists may achieve substantial reductions in the number of benign biopsies and misdiagnosed cancers.

The levels of postresidency mammographic experience among the radiologists in this study ranged from 29 years to 6 months ($R_1 > R_2 > R_3 > R_4$). Figures 4–7 suggest that all radiologists are likely to benefit substantially from access to the mapped-database diagnostic system regardless of their experience. This is important, because radiologists vary widely in their diagnostic skills—even among those who rate themselves as "experts" (31). Whether the size of the benefit correlates with the amount of experience, however, is not clear from Figures 4–7. (It is interesting that the performance of the aided R_2 exceeded that of the aided R_1, even though the experience of R_1 was greater.)

The results of this study suggest that a properly designed interface between a human reader and a proved database of mammographic images may enable less experienced readers to exceed the performances of unaided, highly skilled readers—without the need for time-consuming training on feature extraction as exemplified by Getty et al (19). Furthermore, our diagnostic system represents an improvement over earlier systems (17,19) by automating the selection of visual features.

This study was limited, however, by the quality of the monitors used for viewing the images, the size and comprehensiveness of the mammographic database, the lack of full-field and earlier views, the restriction of the lesions to microcalcifications, and a possible "reading-order effect" associated with the close succession of unaided and aided diagnoses (32). Our next investigation of the mapped-database diagnostic system will include several enhancements to overcome these limitations. The images will be viewed on state-of-the-art, high-resolution radiographic monitors, and the number of cases will be increased. The tested images will also include full-field craniocaudal and mediolateral oblique or lateral views of each breast, and the lesions

Table 5
Statistical Significance of Changes in Performance

	Unaided Radiologist (%)		Aided Radiologist (%)		Change in Sensitivity		Change in Specificity	
Reader	Sensitivity	Specificity	Sensitivity	Specificity	Change (%)	*P*	Change (%)	*P*
R_1	47.8	73.7	69.6	86.0	+21.8	<.01	+12.3	.12
R_2	65.2	68.4	87.0	82.5	+21.8	<.01	+14.1	<.05
R_3	52.2	68.4	65.2	80.7	+13.0	.09	+12.3	.07
R_4	69.6	50.9	82.6	68.4	+13.0	<.05	+17.5	<.05

will include both masses and microcalcifications. In addition, the aided and unaided diagnoses will be separated by at least 1 month.

ACKNOWLEDGMENTS

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CURRICULUM VITAE

Name: Jack Sklansky **Birthdate**: November 15, 1928

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Education:

Eng.Sc.D., 1955,	Columbia University
M.S.E.E., 1952,	Purdue University
B.E.E., 1950,	The City College of New York

Honors and Awards:

Fellow of the Institute of Electrical and Electronics Engineers, for contirbutions to digital pattern classification and medical applications."

Fellow of the International Association for Pattern Recognition, "for contibutions to pattern recognition, machine, and medical imaging, and service to the IAPR."

Award for Research Excellence, School of Engineering, UCI
Annual Award of the Pattern Recognition Society
Tau Beta Pi
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Who's Who in America

Professional Interests:

Medical imaging, computer-aided diagnosis, automatic pattern recognition, machine vision, intelligent machines, neural networks, computer engineering, biomedical engineering.

Academic Appointments:

Professor of Radiology, Charles R. Drew University of Medicine and Science, Los Angeles, 1996-present

Research Professor of Electrical and Computer Engineering and of Radiological Sciences, University of California, Irvine, 1994-present

Research Professor of Radiological Sciences, UCI, 1971-present

Professor of Electrical Engineering, UCI, 1969-present

Professor of Information and Computer Science, UCI, 1969-1989

Chairman of Electrical Engineering: 1978-1979

Associate Professor of Electrical Engineering, UCI, 1966-1969

Professional Service and Activities:

Member of the Radiological Society of North America

Fellow of the Institute of Electrical and Electronic Engineers

Member of Advisory Committee for MTAC 2000 – The Multimedia Conference for the Arts and Sciences

Chair of Welfare Committee of UCI Emeritae/I Association

Co-Chair of International Workshop on Digital Video for Intelligent Systems, December 1993.

Member of Governing Board of the International Association of Pattern Recognition (IAPR)

Chairman of the IAPR King-Sun Fu Award Committee

Member of Editorial Board of *Machine Vision and Applications*

Associate Editor of *Pattern Recognition*

Co-editor of Special Issue of the Journal of the Optical Society of America A on "Pattern Recognition and Image Understanding"

Member of Organizing Committee and Program Co-Chairman of the International Symposium on Computer-Aided Radiology, held in Anaheim, California in June 1990.

Member of Organizing Committee of the 1990 International Symposium on Computer-Assisted Radiology.

Member of Program Committee of the Third Int. Conf. on Computer Analysis of Images and Patterns, Leipzig, German Democratic Republic, September 1989

Member of Program Committee of 1989 International Symposium on Computer-Assisted Radiology, June 1989

Member of Adv. Board of IEEE Trans. on Pattern Analysis and Mach. Intelligence.

Co-chairman of U.S. Army Conference on Pattern Recognition in Advanced Missile Systems, Huntsville, Alabama, November 1988.

Co-chairman of Program Committee for SPIE Conference on Hybrid Image and Signal Processing, Orlando, Florida, April 1988.

Reviewer for the following journals:

IEEE Transactions on Medical Imaging
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Machine Vision and Applications
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International Journal of Pattern Recognition and Artificial Intelligence
IEEE Transactions on Systems Man and Cybernetics
Journal of the Optical Society of America A

Reviewer for the following funding agencies:

National Institutes of Health
National Science Foundation
U.S. Army Medical Research and Materiel Command
University of California MICRO program
National Research Council of Canada

Reviewer of books for the following publishers:

IOP Publishing Ltd., Philadelphia
Springer-Verlag, New York
John Wiley, New York
Addison-Wesley, Reading, Massachusetts

Ph. D. Advisees (names, title of dissertation, year of graduation, current position if known) :

Brian Lofy, "Segmenting and Matching of Aerial Images Acquired by Different Sensors," 1999: Senior Engineer, Marconi Corporation, San Diego, California.

Eric Y. Tao, "Database-Aided Diagnosis in Digital Mammography," 1998: Assistant Professor, Institute of Communication Science and Technology, California State University, Monterey Bay, California

Mark Vriesenga, "Genetic design of pattern classifiers," 1995: Senior Engineer, Marconi Corporation, San Diego, California.

L.V. Tran, "Quantitative Biplane Angiography", 1991: Research Engineer, Northrop Corporation, Anaheim, California

Y. Moon, "Multicomputer architectures for image analysis," 1990: Assistant Professor, Korea Academy of Industrial Technology, Seoul, Korea

D. Gutfinger, "Mixed Adaptation -- a Theory for Designing Robust Classifiers," 1990: Student at UCI College of Medicine

Y. Park , "Linear Tree Classifiers" 1990, Assistant Professor, Kyung Hee University, Suwon Campus,Yongin, Kyungkido, Korea

W. W. Siedlecki, "Feature selection for large scale classifiers," 1988: Vice President for Research, P-Logic Corporation

K. Kitamura, "Estimating the transverse areas and boundaries of coronary arteries in three dimensions," 1987: Research Engineer, Nippon Steel Corporation

P. E. Chandler, "A multiple scattering model for pulse propagation within velocity inhomogeneous, lossy, and refractive media," 1986

T. V. Nguyen, "Three-dimensional reconstruction of the medial axes of coronary arteries from single-view angiograms," 1986: President, Multisignal Technology Corporation; Professor, California State University, Long Beach, California

I. Foroutan, "Feature selection for piecewise linear classifiers," 1985: Manager of Circuit Automation, Hughes Aircraft Co.

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D. Petkovic, "A computer system for coarse-fine detection of pulmonary nodules in chest radiographs," 1983: Manager of Department of Advanced Algorithms, Architectures, and Applications, IBM Almaden Research Center

L. A. Ferrari, "Recursive binary-valued image filters," 1980: Associate Professor of Electrical and Computer Engineering, Chairman of Department of Electrical and Computer Engineering, UC Irvine

E. J. Pisa, "Computing the geometry of the rib cage from two chest radiographs," 1979: Vice President of Research and Development, Ivac Corporation

H. Wechsler, "Automatic Detection of Rib Contours in Chest Radiographs," 1975: Professor of Computer Science, George Mason University

D. H. Ballard, "Hierarchic Recognition of Tumors in Chest Radiographs," 1974: Professor of Computer Science, University of Rochester

P. J. Nahin, "A parallel machine for describing and classifying silhouettes," 1972: Associate Professor of Electrical Engineering, University of New Hampshire

P. M. Merryman, "Dynamics of multidimensional Markov learning," 1972: Senior System Engineer, Ultrasystems, Inc.

G. N. Wassel, "Training a linear classifier to optimize the error probability," 1972: Professor of Electrical Engineering, Cal Poly University, San Luis Obispo, California

H. R. Ramanujam, "A stopping rule for threshold learning," 1970: Principal Engineer, McDonnell Douglas Corp.

M. S. Advisees:

Chester Ornes, " A Neural Classifier for Database-Aided Decisions," 1997.

J. Ribas-Corbera, "Image Data Compress and Interframe Interpolation of Cinematic Sequences," 1992.

M. R. Vriesenga, "Colored Illumination for Maximizing Contrast in Machine Vision," 1991.

R. Agarwal, "Optical Flow from Clusters in Velocity Space," 1991.

E. M. Hertzberg, "Quantitative Analysis of Magnetic Resonance Images," 1991.

J. B. Bartels, "Analysis of Random and Systematic Errors in T_i Measurement with Gradient Echo Magnetic Resonance Imaging," 1990.

S. R. Reuman, "Computing Albedo, Illumination, and Optical Flow with Spacetime-Adaptive Bandpass Filtering," 1988.

J. J. Duffy, "Time Varying System Feedback Design," 1988.

N. Iliev, "Failure Isolation in Linear Stochastic Systems -- the Associative Recall Approach," 1987.

R. F. DeShetler, "Finding the Polyhedra Formed by the Hyperplanes of a Piecewise Linear Classifier," 1986.

N. P. DeMesa, "Petri Net Analysis," 1986.

P. E. Chandler, "A Multiple Scattering Model for Pulse Propagation within Velocity Inhomogeneous, Lossy, and Refractive Media," 1986.

S. V. Hung-Leo, "Computer-Aided Design of Multiple-Class Piecewise Linear Classifiers, 1983.

F. Towfiq, "Piecewise Linear Detection of Curved Edges, 1980.

M. D. McNeil, "Digital Preprocessing of Low Contrast, Wide Dynamic Range Images," 1975.

T. Miyatake, "Compute-Film System for Contrast Enhancement," 1972.

D. V. Smith, "Dynamic Behavior of Time-Varying Threshold Learning Processes," 1968.

Visiting Scholars:

Professor Minechi Kudo, Hokkaido University, Sapporo, Japan, 9 months, 1996.

Professor Leon Bobrowski, Polish Academy of Science, Fulbright Scholar, Poland, 1 year, 1994-1995.

Oliver Paetz, RW Technische Hochschule, Germany, 10 months, 1994-1995.

Matthias Kroemer, RW Technische Hochschule, 6 months, 1995-1996.

Ariela Kamin, Technion -- Israel Institute of Technology, Israel 1990 -1991

Akio Shio, Nippon Telegraph and Telephone Corporation, Japan - 1.5 years 1989-1991

Professor Kalman Peleg, Technion -- Israel Institute of Technology, Israel - 5 months, 1990

Professor Peter Jensch, The University of Oldenburg, West Germany -6 weeks, 1989-1990

Ryuji Nishimura, Hitachi Ltd., Japan - 1.5 years 1989 - 1990

Dr. Thomas Tolxdorff, Rheinisch-Westfalischen Technischen Hochscule, West Germany - 4 weeks, 1989

Dr. Leon Bobrowski, Institute of Biocybernetics and Biomedical Engineering, Poland, 3 weeks, 1989

Djordije Jankovic, Boris Kidric Institute, Yugoslavia - 3 months, 1989

Professor Mirek Pawlak, The University of Manitoba, Canada - 2 months, 1989

Hideaki Doi, Hitachi Ltd, Japan - 1 year, 1988-1989

Professor Adam Krzyzak, Concordia University, Canada - 1 month, 1988.

EXTRAMURAL FUNDING SINCE 1987

PROGRAM TITLE	DATES	AGENCY	MONETARY LEVEL
Database-Aided Diagnosis in Digital Mammography	1999-03	U. S. Army Medical Research and Materiel Command	$1,928,000
Database-Aided Telemammography	2000-02	California Telehealth & Telemedicine Center	$100,000
Computer-Aided Diagnosis In Digital Mammography	1997-99	California Breast Cancer Research Program	$214,000
Biologically Inspired Intelligent Classifiers	1992-96	NSF	$ 330,000

Landmark Detection	1997-98	Naval Air Warfare Center	$25,000
Line Detection and Genetic Feature Selection	1995-96	ONR	$ 135,000
Genetic Algorithms for Target Recognition	1993-94	Naval Air Warfare Center	$ 20,000
Digital Video for Intelligent Systems	1993-94	NSF	$ 25,000
Target Recognition	1992-93	UC MICRO/Loral	$ 53,000
Computer Vision	1989-92	NTT (Nippon Telegraph and Telephone Corporation)	$ 120,000
Automated Tissue Production	1989-92	BARD (Binational Agricultural Research & Development Fund)	$ 129,000
Neural Learning	1989-91	DARPA	$ 300,000
Image Processing Architectures	1989-90	Rockwell/Micro	$ 34,000
Computer Vision	1988-90	Hitachi	$ 55,000
Automatic Pattern Classification	1987-90	Army Research Office	$ 140,000
Discretionary Research		Hughes Aircraft	$ 10,000

PUBLICATIONS

Books:

Pattern Classifiers and Trainable Machines (with G. Wassel), Springer-Verlag, 1981

Books edited:

1. *Biomedical Images and Computers* (co-edited with J. C. Bisconte), Springer-Verlag, Heidelberg, 1982.

2. *Proceedings of the Symposium on Computer-Aided Diagnosis of Medical Images* (editor), IEEE Computer Society, November 1976.

3. *Pattern Recognition: Introduction and Foundations* (editor), Dowden, Hutchinson, and Ross, Stroudsburg, PA, 1973.

Book Chapters and Articles:

1. "Large-Scale Feature Selection" (with W. Siedlecki), *Handbook of Pattern Recognition & Computer Vision*, edited by C.H. Chen, L.F. Pau, P.S.P Wang, World Scientific, 1993, Chapter 1.3, pp. 61-123.

2. "Biomedical Image Analysis" (with P. V. Sankar and R. J. Walter), *Handbook of Pattern Recognition and Image Processing*, ed. by Young and Fu, Chapter 26, Academic Press, 1986.

3. "Two-Resolution Detection of Lung Tumors in Chest Radiographs," (with D. Petkovic), *Multiresolution Image Processing*, edited by A. Rosenfeld, Springer-Verlag, 1983, pp. 365-378.1

4. "The Use of Markov Random Fields as Models of Texture" (with Martin Hassner), *Image Modeling*, edited by A. Rosenfeld, Academic Press, 1980, pp. 185-198. Also: Computer Graphics and Image Processing, Vol. 12, 1980, pp. 357-370.

5. "Toward Computed Detection of Nodules in Chest Radiographs," *Real Time Medical Image Processing*: edited by M. Onoe, K. Preston, Jr., A. Rosenfeld, Plenum Press, New York, 1980, pp. 53-59.

6. "Biomedical Image Analysis," *Issues in Digital Image Processing*, edited by R. M. Haralick and J. C. Simon, published by Sijthoff and Noordhoff, Alphen, The Netherlands, 1980, pp. 291-311.

7. "Image Segmentation and Feature Extraction," *Digital Image Processing and Analysis*, edited by J. C. Simon and A. Rosenfeld, Noordnoff International Publishers, Groningen, The Netherlands, 1977.

8. "Boundary Detection in Medical Radiographs," *Digital Processing of Biomedical Images*, edited by K. Preston and M. Onoe, Plenum Press, New York, 1976, pp. 309-322.

9. "Time-Varying Threshold Learning," *Proceedings of 1966 Joint Automatic Control Conference, University of Washington*, Seattle, Washington, August, 1966, pp. 33-37. Also: *Cybernetic Problems in Bionics*, ed. by H.L. Oestreicher and D. R. More, Gordon and Breach Science Publishers, New York, 1968, pp. 687-695.

Refereed journal articles:

1. J. Sklansky, Eric Y. Tao, M. Bazargan, C.J. Ornes, R.C. Murchison, S. Teklehaimanot, "Computer-Aided, Case-Based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications," *Academic Radiology*, Vol. 7, No. 6, June 2000, pp. 395-405.

2. Kenneth R. Hoffmann Ph.D., Andreas Wahle Ph.D., Claire Pellot-Parakat Ph.D., Jack Sklansky Eng.Sc.D., Milan Sonka, Ph.D., "Biplane Xray Angiograms, Intravascular Ultrasound, and 3D Visualization of Coronary Vessels," submitted to *International Journal of Cardiac Imaging*, July 1999.

3. C. Ornes, J. Sklansky, "A Visual Neural Classifier," *IEEE Trans. on Systems, Man, and Cybernetics*, Part B, Vol. 28, No. 4, August 1998, pp. 620-625.

4. Chester Ornes, Jack Sklansky, "A Neural Network that Visualizes What It Classifies," *Pattern Recognition Letters*, Vol. 18, 1997, pp. 1301-1306.

5. B-B Chai, T. Huang, X. Zhuang, Y. Zhao, J. Sklansky, "Piecewise linear classifiers using binary tree structure and genetic algorithm," *Pattern Recognition*, Vol. 29 No. 11, 1996, pp. 1905-1917.

6. " Genetic Selection and Neural Modeling of Piecewise Linear Classifiers" (with M. Vriesenga), *International Journal of Artificial Intelligence and Pattern Recognition*, August 1996.

7. "Colored Illumination for Enhancing Discriminability in Machine Vision" (with M. Vriesenga, G. Healey), *Journal of Visual Communication and Image Representation*, Vol. 6, No. 3, September 1995, pp. 244-255.

8. "Linear Classifiers by Window Training" (with L. Bobrowski), *IEEE Transactions on Systems, Man and Cybernetics, Vol. 25*, No. 1, Jan. 1995, pp. 1-9.

9. J. Sklansky, "Toward Quantitative Coronary Angiography," *Proceedings of the Japanese Association of Medical Imaging Technology*, Vol. 12, No. 4, July 1994, pp. 295-305.

10. "Reconstructing the 3-D Medial Axes of Coronary Arteries in Single-View Cineangiograms" (with T. V. Nguyen), *IEEE Transactions on Medical Imaging*, Vol. 13, No. 1, March 1994, pp 61-73.

11. "Interframe Interpolation of Cinematic Sequences" (with J. Ribas-Corbera), *Journal of Visual Communication and Image Representation*, Vol. 4, No. 4, December 1993, pp. 392-406.

12. "Graph-based Thinning for Binary Images" (with S. Suzuki, N. Veda), *International Journal of Pattern Recognition and Artificial Intelligence*, Special Issue on Techniques for Thinning Digitized Patterns, 1993, pp. 1009-1030.

13. L.V. Tran, R.C. Bahn, J. Sklansky, "Reconstructing the Cross Sections of Coronary Arteries from Biplane Angiograms", *IEEE Trans. on Medical Imaging*, Vol. 11, No. 4, Dec. 1992, pp. 517-529.

14. "Flexible Mask Subtraction for Digital Angiography" (with L.V. Tran), *IEEE Trans. on Medical Imaging*, Vol. 11, No. 3, September 1992, pp. 407-415.

15. "Robust Classifiers by Mixed Adaptation" (with D. Gutfinger), *IEEE Transactions on Pattern Analysis and Machine Intelligence*, Vol. 13, No. 6, June 1991, pp. 552-567.

16. "Automated Design of Linear Tree Classifiers" (with Y. Park), *Pattern Recognition*, Vol. 23, No. 12, 1990, pp. 1393-1412.

17. "A note on genetic algorithms for large-scale feature selection" (with W. Siedlecki) *Pattern Recognition Letters*, 1989, pp. 335-347.

18. "Macropipelined multicomputer architecture for image analysis" (with Y. Moon, N. Bagherzadeh), *Journal of the Optical Society of American A*, 1989.

19. "Automated design of multiple-class piecewise linear classifiers " (with Y. Park), *Journal of Classification*, 1989, pp. 195-222.

20. "Mapping techniques for exploratory pattern analysis," (with W. Siedlecki and K. Siedlecka), *Pattern Recognition and Artificial Intelligence*, edited by E.S. Gelsema and L.N. Kanal, Elsevier Science Publishers B. V. (North-Holland), 1988, pp. 277-299.

21. "Bottlenecks to effective application of machine vision -- a discussion," *Machine Vision: Algorithms, Architectures, and Systems*, edited by H. Freeman, Academic Press, 1988, pp. 187-192.

22. "Estimating the 3-D skeletons and transverse areas of coronary arteries from biplane angiograms," (with K. Kitamura), *IEEE Transactions on Medical Imaging*, September 1988, pp. 173-187.

23. "On automatic feature selection," (with W. Siedlecki), *International Journal on Pattern Recognition and Artificial Intelligence*, Vol. 2, No. 2, August 1988, pp. 197-220.

24. "Overview of mapping techniques for exploratory pattern analysis," (with W. Siedlecki, K. Siedlecka), *Pattern Recognition*, Vol. 21, No.5, pp. 431-438, 1988.

25. "Experiments on mapping techniques for exploratory pattern analysis" (with W. Siedlecki, K. Siedlecka), *Pattern Recognition*, Vol. 21, pp. 431-438, 1988.

26. "Real-time scene understanding and vision automation -- a brief overview," (with K. H. Kim), ed. by Francis J. Corbett, *Proceedings of SPIE -- The International Society for Optical Engineering*, Vol. 755, Image Pattern Recognition Algorithm Implementations, Techniques, and Technology, January 1987, pp. 126-131.

27. "Recursive algorithms for implementing digital image filters," (with L. Ferrari, P. V. Sankar, S. Shinnaka), *IEEE Transactions on Pattern Analysis and Machine Intelligence*, Vol. PAMI-9, No. 3, May 1987, pp. 461-466.

28. "Feature selection for automatic classification of non-Gaussian data" (with I. Foroutan), *IEEE Trans. on Systems, Man, and Cybernetics*, Vol. SMC-17, No. 3, March/April 1987, pp. 187-198.

29. "Multiple-Order Derivatives for Detecting Local Image Characteristics," (with M. Hashimoto), *Computer Vision, Graphics, and Image Processing*, Vol. 39, 1987, pp. 28-55.

30. "Computing the Skeleton of Coronary Arteries in Cineangiograms," (with T. Nguyen), *Computers and Biomedical Research*, October 1986, pp. 428-444.

31. "Efficient two-dimensional filters using B-spline functions," (with L. Ferrari, P. V. Sankar and S. Leeman), *Computer Graphics and Image Processing*, Vol. 35, 152-169, 1986.

32. "Biomedical Image Analysis," (with P. V. Sankar and R. J. Walter), *Handbook of Pattern Recognition and Image Processing* edited by Young and K-S Fu, Chapter 26, Academic Press, 1986, pp. 629-647.

33. "Elimination of nonpivotal plane images from x-ray motion- tomograms,"(with S. Kawata), *IEEE Transactions on Medical Imaging*, Vol. Mi-4, No. 3, September 1985.

34. "The relative neighborhood graph for mixed feature variables," (with M. Ichino), *Pattern Recognition*, Vol. 8, No. 2, 1985, pp. 161-167.

35. "A note on Duhamel Integrals and Running Average Filters," (with L.Ferrari), *Computer Vision Graphics, and Image Processing*, Vol. 29, pp. 358-360, 1985.

36. "Optimum feature selection by zero-one integer programming," (with M. Ichino), *IEEE Trans. on Systems, Man, and Cybernetics*, Vol. 14, October 1984, pp. 737-746.

37. "A fast recursive algorithm for binary balued two-dimensional filters" (with L. Ferrari), *Computer Vision, Graphics and Image Processing*, Vol. 26, 292-302, 1984.

38. "Minimal Rectangular Partitions of Digitized Blobs," *Computer Vision, Graphics, and Image Processing*, (with L Ferrari, P.V. Sankar), Vol. 28, pp. 58-71, 1984.

39. "Circularly coded x-ray tomography," (with S. Kawata), *Transactions of Applied Optics*, Vol. 23, No. 10, May 15, 1984.

40. "Scan-along polygonal approximation for data compression of electrocardiograms," (with M. Ishijima. S. Shin, G. Hostetter), *IEEE Trans. on Biomedical Engineering*, November 1983, pp. 723-729.

41. "Two-resolution detection of lung tumors in chest radiographs," (with D. Petkovic), *Multiresolution Image Processing*, edited by A. Rosenfeld, Springer-Verlag, 1983, pp. 365-378.

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46. "Skeleton generation from x,y boundary sequences of biological objects" (with B. Shapiro, E. J. Pisa), *Computer Graphics and Image Processing*, 1981, pp. 136-153.

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50. "A gestalt-guided heuristic boundary follower for x-ray images of lung nodules" (with P. V. Sankar), *IEEE Trans. on Pattern Analysis and Machine Intelligence*, Vol. PAMI-4, No. 3, May 1982, pp. 326-331.

51. "Locally trained piecewise linear classifiers," (with L. Michelotti), *IEEE Transactions on Pattern Analysis and Machine Intelligence*, Vol. PAMI-2, No. 2, March 1980, pp. 101-111 .

52. "Fast polygonal approximation of digitized curves" (with V. Gonzalez), *Pattern Recognition*, Vol. 12, pp. 327-331, Pergamon Press, 1980.

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Computer-aided, Case-based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications[1]

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Rationale and Objectives. The purpose of this study was to evaluate the effectiveness of a mapped-database diagnostic system in reducing the incidence of benign biopsies and misdiagnosed cancers among mammographic regions of interest (ROIs).

Materials and Methods. A novel neural network was devised (*a*) to respond to a query ROI by recommending to biopsy or not to biopsy and (*b*) to map each ROI in the database as a dot on a computer screen. The network was designed so that clusters in the array of dots help the radiologist to find proved ROIs visually similar to the query ROI. This mapped-database diagnostic system was restricted to ROIs with visible microcalcifications. The neural network was trained with a stored database of 80 biopsy-proved ROIs.

Results. Four radiologists acting independently on 100 ROIs recommended biopsies for 18, 15, 28, and 18 benign ROIs and misdiagnosed cancers in 11, 12, 7, and eight ROIs, respectively. Interaction with the mapped-database system reduced the numbers of benign biopsies to 11, eight, 18, and 10 cases and of misdiagnosed cancers to eight, seven, four, and three cases, respectively. Statistical analysis indicated that three radiologists achieved significant improvements at $P \leq .02$ and the fourth achieved a substantial improvement at $P \leq .07$.

Conclusion. By using a mapped database of proved mammographic ROIs containing microcalcifications, radiologists may statistically significantly reduce the numbers of benign biopsies and misdiagnosed cancers.

Key Words. Computer-aided diagnosis; digital mammography; microcalcifications.

A critical aspect of mammographic diagnosis is deciding whether to recommend biopsy. Approximately two benign lesions are sampled for biopsy for every malignant lesion detected (1). In a recent study of 2,400 women undergoing mammographic screening during a 10-year period (2), an additional $33 was spent on evaluating false-positive results for every $100 spent on screening. Among the women in that study, the cumulative risk of a false-positive result after 10 mammograms was 49.1%. Thus, it would be highly desirable to reduce the frequency of benign biopsies during mammographic screening without increasing the number of missed cancers.

The objective of this study was to evaluate the effectiveness of a recently devised "mapped-database diagnostic system" in reducing the frequency of benign biopsies and misdiagnosed cancers among mammographic regions of interest (ROIs). The principal difference between this system and earlier computer-aided diagnostic systems for mammography is the facilitation of diagnostic reasoning by a database of proved ROIs. In this study, the presented mammographic images and stored database are restricted to ROIs, and the ROIs themselves are restricted to those revealing apparent microcalcifications.

Interpretation of mammograms consists of two major components: *detection* and *diagnosis*. In detection, the

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radiologist typically examines four full-field views—two views of each breast. In these views, the radiologist may detect one or more ROIs revealing possible lesions. In diagnosis, the radiologist analyzes one or more ROIs to determine whether biopsy should be performed or whether the patient should be recalled for further examination. Thus, analysis of ROIs is an important part of clinical mammography, particularly in establishing a diagnosis. This study focused on the ability of the mapped-database diagnostic system to reduce the number of negative biopsy results and of misdiagnosed cancers associated with the analysis of ROIs.

By restricting the images used in this study to ROIs, thereby excluding the full-breast views, we reduced much of the cost and duration of the experiments, but at the expense of eliminating contextual evidence. A further reduction in cost—and in diagnostic accuracy—was obtained by replacing film mammograms with digital images displayed with a cathode ray tube monitor (3). By anticipating the widespread growth of digital mammography while recognizing these reductions in diagnostic accuracy, this relatively inexpensive study examined the effect of the mapped-database system on diagnostic accuracy during digital mammography.

In the mapped-database system, an artificial neural network responds to a mammographic ROI by recommending, or not recommending, biopsy. In addition, the neural network maps a database of ROIs from proved mammograms onto a two-dimensional display as an aid to establishing a diagnosis. The network does this by mapping each ROI into a dot on a screen and arranging these dots so that they cluster into radiographically similar subclasses. We refer to this representation as a *mapped database*. In addition to producing the mapped database, the neural network partitions the screen into two decision regions: one for a biopsy being recommended, and the other for a biopsy not being recommended. We call the resulting display a *relational map* (4). By annexing this neural network to a means of quickly retrieving and viewing ROIs that are mapped close to the query, the radiologist is given a simple way of conversing with the database to enhance the reliability of the diagnostic decision. Thus, this system amplifies the radiologist's powers of "case-based reasoning" (5) and acts somewhat like a second reader with consensus (6).

This concept led to construction of a mammographic diagnostic system built on the basis of several earlier developments: (*a*) algorithms for detecting and analyzing clusters of microcalcifications (7–10), (*b*) large databases of digitized mammograms (11–15), (*c*) genetic algorithms for high-speed parallel search (16), and (*d*) "visual neural classifiers" (ie, specialized neural networks) that map multidimensional features and multidimensional decision surfaces onto two-dimensional displays (4). We refer to this as a *mapped-database diagnostic system*. The test results reported herein suggest that for mammograms with detectable microcalcifications, this system can provide a new level of reliability for mammographic diagnosis.

The most pertinent earlier work regarding database-aided mammographic diagnosis is that by Swett and his colleagues at Yale University (17). Their mammographic database system, MAMMO/ICON, required a verbal medical history and verbal mammographic descriptors to supplement each mammogram. This system could provide diagnostic advice that depended on semantic similarities of the verbal descriptors and medical histories (18). A shortcoming of this technology, however, was its dependence on verbal descriptors to match information that was essentially pictorial and nonverbal. Among radiologists, there may be considerable variability in the specific words used to describe the pertinent properties of any given mammogram. This variability may impair the reliability of retrieving similar mammograms filed according to verbal descriptors. Another shortcoming was the manual construction of the verbal descriptors for the mammograms, in contrast to the possibility of automatic extraction and counting of key words in text.

Among other published articles on computer-aided diagnosis of mammograms, those by Getty et al (19), Jiang et al (9), and Chan et al (20) are particularly relevant to the present work. Getty et al (19) demonstrated that a checklist of descriptors (ie, "features") combined with a digital classifier could be an effective aid in establishing the diagnosis during mammography. These features, as in our experiment, were for the most part descriptors of a "focused abnormality" (ie, the equivalent of ROI as used here). The protocol for aiding the radiologist included a computer-alone reading, which was followed with a second reading by the radiologist (analogous to a double reading with consensus). A second contribution by Getty et al was the demonstration that a carefully selected set of features, when coupled with a session to train radiologists to estimate these features, could enable computer-aided generalists to read film mammograms almost as well as highly skilled specialists. Jiang et al (9) demonstrated the potential of automatically extracting features from microcalcifications, coupled with an artificial neural network, for computer-aided diagnosis. The methods in both of these studies (9,19), however, still required substantial human involvement in the computer-aided procedure. In the method of Getty et al (19), each radiologist estimated the numeric level of intensity or level of confidence for the existence of each feature; in the method of Jiang et al (9), the location of each microcalcification was determined manually. This

amount of human involvement likely makes these techniques impractical for clinical use.

Chan et al (20) restricted human involvement to identifying in each view an ROI enclosing a mass. This level of human involvement is likely to be practical during clinical applications, because finding ROIs is part of the usual procedure for interpreting mammograms. As in the method of Getty et al (19), the radiologist-reader in the method of Chan et al (20) was asked to make a final estimate regarding the likelihood of malignancy in a presented mammogram after first performing an unaided estimation and then receiving the computer's estimate. In that study, the performance of the computer alone was comparable to that of the best performing unaided radiologist-reader and to the performance of six aided radiologist-readers as a group.

MATERIALS AND METHODS

A retrospective study of the mapped-database system was performed during June 1998. The ROIs included in this study were restricted to those exhibiting microcalcifications. For this study, we acquired a database of 200 ROIs from 138 proved cases. Biopsy results were included with each ROI. Four radiologists from the clinical faculty of the Department of Radiology at King/Drew Medical Center (KDMC) read the digitized images in this study. None of these radiologists was familiar with the cases, and all of them were certified for mammography by the U.S. Food and Drug Administration. Their postresidency experience in reading mammograms was 29 years, 10 years, 5 years, and 6 months; these readers are referred to as R_1, R_2, R_3, and R_4, respectively.

The ROIs in the database were excised from digitizations of film mammograms provided by KDMC and by the University of California at Los Angeles (UCLA) Iris Cantor Center for Breast Imaging. In all cases associated with these mammograms, either biopsy or follow-up with subsequent mammography was performed. From these mammograms, all 138 cases that revealed microcalcifications were selected for this study. Fifty-two cases were from KDMC, and 86 were from UCLA. The selected mammograms were digitized at KDMC on a scanner-digitizer (Lumiscan 85; Lumisys, Sunnyvale, Calif) at a pixel width of 50 μm and a pixel depth of 12 μm.

For each film mammogram, the location of an abnormality containing a cluster of microcalcifications was provided in the medical record that accompanied the image. From this information, we constructed a 512×512-pixel ROI enclosing each designated cluster of microcalcifications. This construction yielded 160 ROIs. No two ROIs in this set were views of the same lesion. To each ROI we applied an automatic microcalcification detector and segmenter that was developed during an earlier study (7). An additional 40 normal ROIs were also added to this database, thereby making a total of 200 ROIs in this study. These normal ROIs were included to ensure that readers would have the impression that not all ROIs in the set used to test the system (described later) were abnormal. The normal ROIs were obtained from cases involving patients who did not undergo biopsy and were not recalled during a period of at least 18 months. Within each of these cases, the normal ROI was selected arbitrarily.

Of the abnormal ROIs (ie, those containing microcalcifications), 64 were proved at biopsy to be benign, 49 were proved at biopsy to be malignant, and 47 were proved at follow-up to be benign (ie, both the ROI and the follow-up findings did not produce a recommendation for biopsy). At least 18 months elapsed between two successive examinations, and none of the radiologists on our reading panel had seen these ROIs before this study. One radiologist (R_1) partitioned the 200 ROIs into groups such that ROIs in the same group were visually similar. We refer to these groups as *perceptual groups*. No restriction was placed on the number of perceptual groups, although the radiologist (R_1) was informed that eight groups were formed by another radiologist during another set of ROIs in an earlier experiment (21). The radiologist (R_1) partitioned the 200 ROIs into the following 12 groups: (*a*) amorphous with mass, (*b*) lobular and ductal, (*c*) amorphous, (*d*) pleomorphic and scattered, (*e*) lobular, (*f*) granular, (*g*) casting, (*h*) punctate scattered, (*i*) linear ductal, (*j*) vesicular, (*k*) oil cyst, and (*l*) no visible abnormality.

Computer-aided reading of the test set by the reading panel was performed more than a month after partitioning of the ROIs into perceptual groups. The intent of this 1-month delay was to suppress the memory of the 200 ROIs in the radiologist who partitioned them into the perceptual groups.

The database was then divided into two sets, D and T, each of which consisted of 100 ROIs. D was used for the design of the diagnostic system, and T was used for testing of the system. The 160 abnormal ROIs were randomly partitioned several times into two equal parts, D_A and T_A, until a (D_A, T_A) pair was found such that D_A and T_A each contained at least two ROIs from each perceptual group. (Ensuring representation of at least two ROIs from each perceptual group, however, may have biased the diagnostic system somewhat in favor of the neural network. On the other hand, not achieving this representation would have biased the study against the neural network.) D_A consisted of 54 benign and 26 malignant ROIs. T_A consisted of 57 benign and 23 malignant ROIs. Because no two ROIs were images of the same lesion, all lesions in T

Table 1
Features Extracted from Microcalcifications and Regions of Interest

Feature	Symbol	Formula	Clinical Importance
Area	*A*	Number of pixels in the calcification labeled ≥ 0	Large calcification may suggest a benign abnormality.
Perimeter	*P*	Number of pixels in central boundary (label = 0)	Large calcification may suggest a benign abnormality.
Irregularity	*I*	A/P^2	Irregular boundary may suggest a malignant abnormality.
Mean intensity	*MI*	Average brightness of pixels labeled ≥ 0	Bright calcification may suggest a benign abnormality.
Standard deviation of intensity	*SI*	Standard deviation of pixels labeled ≥ 0	Large *SI* may suggest an irregular density and malignancy.
Mean of exterior intensity	*ME*	Average brightness of pixels within 5 pixels from the calcification	Large *ME* may suggest a dense and malignant tissue.
Standard deviation of exterior intensity	*SE*	Standard deviation of pixels within 5 pixels from the calcification	Large *SE* may suggest a malignant tissue.
Contrast	*C*	$\|MI - SI\| - MI$	Large contrast may suggest a benign abnormality.
Sharpness of boundary	*SH*	Average change in brightness between pixels labeled 0 or 1 and those labeled −1 or −2	Large *SH* may suggest a benign abnormality.
Inner shell contrast	B_1	Average change in brightness between pixels labeled 2 and those labeled 1	Large B_1 may suggest a benign abnormality.
Center shell contrast	B_0	Average change in brightness between pixels labeled 1 and those labeled 0	Large B_0 may suggest a benign abnormality.
Outer shell contrast	B_{-1}	Average change in brightness between pixels labeled 0 and those labeled −1	Large B_{-1} may suggest a benign abnormality.
Exterior shell contrast	B_{-2}	Average change in brightness between pixels labeled −1 and those labeled −2	Large B_{-2} may suggest a benign abnormality.
Concavity index	*CI*	Area of region between the calcification and its convex hull	Large *CI* may suggest a malignancy.
Shape signature	*SG*	$\left[\int \lvert r(\theta) - R \rvert d\theta\right] / R$, where *r* is radial distance of boundary from centroid, *R* is the mean of *r*, and θ is orientation of *r*	A large *SG* may suggest benign tissue.
Aspect ratio	*R*	Ratio of maximum central diameter to minimum central diameter	Large *R* may suggest a malignancy.
Count	*N*	Number of calcifications	Large count may suggest malignancy.
Structural index	*S*	$1 - d\sqrt{(N/AC)}$, where *d* is the average distance of the closest calcification and *AC* is area spanned by cluster	Large *S* indicates nonuniform distribution of microcalcifications and, hence, may suggest malignancy.

were distinct from all lesions in D. The 40 normal ROIs were partitioned several times into two equal parts, D_N and T_N, until a (D_N, T_N) pair was found such that D_N and T_N had similar distributions in the mapped feature space. The final design set D was the union of D_A and D_N. The final test set T was the union of T_A and T_N. These procedures were performed to ensure the design set was representative of the types of abnormalities occurring in the test set. As mentioned, the normal ROIs were included to ensure the readers would have the impression that not all ROIs in T were abnormal. Because diagnostic (rather

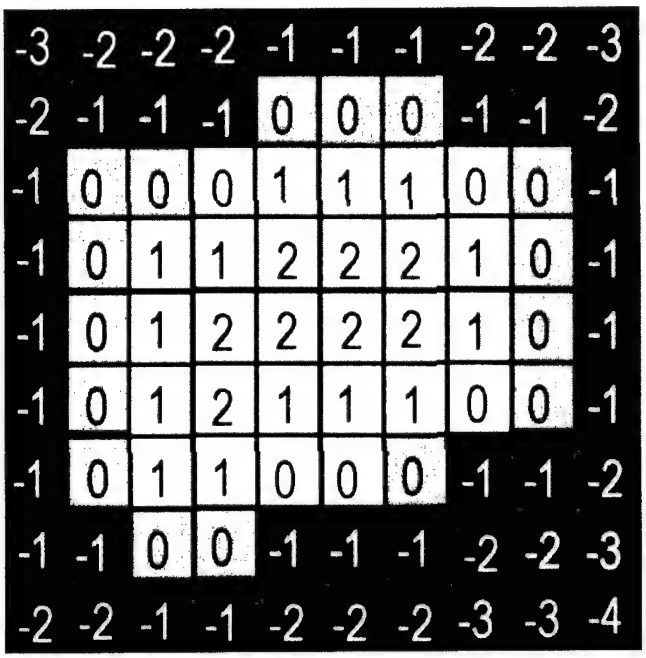

Figure 1. Numeric labeling for the pixels of a digital model representing a typical microcalcification. The label of each pixel is the number of pixel displacements of that pixel from the medial axis of the boundary of the microcalcification. Thus, 0 denotes a pixel on the medial axis of the boundary, 1 a pixel just inside the boundary, –1 a pixel just outside the boundary, and –2 a pixel just outside the –1 region.

than detection) efficacy was paramount in this study, the mapped-database system in this study was designed to analyze only the abnormal ROIs. Consequently, readings of the normal ROIs were not included in our calculations of specificity, sensitivity, and other measures of performance.

From each abnormal ROI, 18 candidate features were extracted. Each candidate feature was designed to reflect one or more properties of calcifications (or groups of calcifications) that are meaningful to the radiologist. These features were based on the American College of Radiology's Breast Imaging Recording and Data System (BI-RADS) descriptors for interpreting mammograms, the book by Lanyi (22), and discussions with the radiologists on our panel. Unfortunately, most BI-RADS descriptors are too subjective for encoding into computer-executable formulas. Consequently, the features we extracted were inspired by, but not necessarily a direct implementation of, the BI-RADS descriptors. A formulation and brief clinical justification for each of these features are given in Table 1. In the first two columns of this table, a name and a mathematical symbol denote each feature. A formula for each feature is given in the third column. The fourth column contains a brief description of the clinical importance of the feature. Some of the formulas refer to numerical pixel labels –2, –1, 0, and 1. The label on each pixel P is the number of pixel displacements of P from the boundary of a calcification. The label 0 denotes a pixel on the boundary, 1 denotes a pixel just inside the boundary, –1 denotes a pixel just outside the boundary, and –2 denotes a pixel just outside the –1 region. These labels are illustrated in Figure 1, which shows a digital model of a typical microcalcification.

Starting from this set of candidate features, a genetic algorithm searched for those subsets of features that were most effective in discriminating malignant from benign cases in the database. This algorithm was designed in accordance with the genetic feature selector described by Siedlecki and Sklansky (23). In this algorithm, each candidate subset is represented by a binary string (ie, a sequence of 0s and 1s). The value (0 or 1) of the nth element of the string indicates whether the nth feature belongs to the candidate subset. We refer to this string as a *chromosome*. A population of 100 chromosomes was transformed by an evolutionary process consisting of mutation, mating, and reproduction to form a sequence of new populations or "generations" under the guidance of a penalty function that accounted for the k-nearest-neighbor discriminability of the feature vectors in each feature subset and for the number of features in the subset. The sizes of the new populations were kept constant at 100. This evolutionary process also optimized the value of k. To ensure an acceptably low rate of misdiagnosed cancers, the penalty function gave seven times as much weight to misdiagnosing a cancer as to recommending a biopsy that was benign. (The weight was chosen empirically so that the nearest-neighbor classifier would produce only one or two missed cancers on the data set.) This algorithm selected the following four features: (*a*) mean area, (*b*) mean aspect ratio, (*c*) mean irregularity (ie, noncircularity), and (*d*) number of microcalcifications. Another algorithm extracted these four features from each ROI, thus forming a four-dimensional *feature vector* as a descriptor of that ROI.

A five-layer neural network was constructed in accordance with the architecture and the design principles described by Ornes and Sklansky (24). Each node in this architecture represented an artificial neuron that consisted of a weighted summation followed by a sigmoidal activation function. The first layer consisted of four input neurons, one for each selected feature. The second and third layers consisted of three and two neurons, respectively, to reduce the dimensionality of feature space. The two-neuron layer produced x and y coordinates (one from each of the two neurons) to represent each ROI as a dot on a relational map. For each ROI in the design set, this dot was labeled to indicate whether the biopsy was benign or malignant. The two

neurons in the fifth layer classified each feature vector as either "biopsy recommended" or "biopsy not recommended." (The neuron producing the larger of the two outputs determined the class of the feature vector.) By entering every permissible pair of map coordinates at the input to the fourth layer, the fifth layer thus produced a relational map in which all pixels were labeled as either biopsy recommended or biopsy not recommended.

Using the four features selected by the genetic algorithm, the neural network was trained by backpropagation (ie, a form of gradient descent in the space formed by the weights at the inputs to the neurons) on the design set D_A, thereby producing the trained neural network NN(D_A) (4). In accordance with our design philosophy for this study, the neural network was trained only on abnormal ROIs. The biopsy outcomes (ie, benign and malignant) in the database were the desired output classes in the trained neural network, which produced a two-dimensional map of D_A and a near-optimal partition of this map into two decision regions. These decision regions were associated with the decisions of biopsy recommended and biopsy not recommended. The training was stopped when the mean square error converged to a nearly constant value. This design strategy, and the relatively low error rate of the neural network on the test set T, encouraged us to believe that the network was then adequately trained.

The boundary separating the decision regions is referred to as a *decision curve*. The decision curve is substantially smoother than the variability of the data, which is the result of the averaging produced by the backpropagation training and the small number of neurons compared with the number of feature vectors in the training set. The neural network tends to produce decision regions that are responsive to statistical models of the training data rather than to the training data itself. Specifically, the training algorithm minimized a weighted sum-of-squared-error function, which yielded outputs that were estimates of Bayesian posterior probabilities that the input vector belonged to the corresponding class (ie, biopsy recommended or biopsy not recommended). Thus, the decision curve produced by the neural network tends to "generalize" the training data and, thereby, to make good decisions on future data not included in the training set (25).

The trained neural network displayed the query and the ROIs in D_A as dots, with each dot being located by the x and y coordinates produced by the two neurons (one coordinate from each neuron) at the two-neuron layer of the network. We refer to the space spanned by x and y as the *mapped feature space* and to the map of D_A as a *mapped database*. The map of D_A and its decision regions are depicted in Figure 2. We call this a *relational map*. Here, the black region represents biopsy recommended, and the white region represents biopsy not recommended. The decision curve is the boundary between the black and the white regions. The symbols O and X denote benign and malignant feature vectors, respectively. The symbol ■ denotes a query.

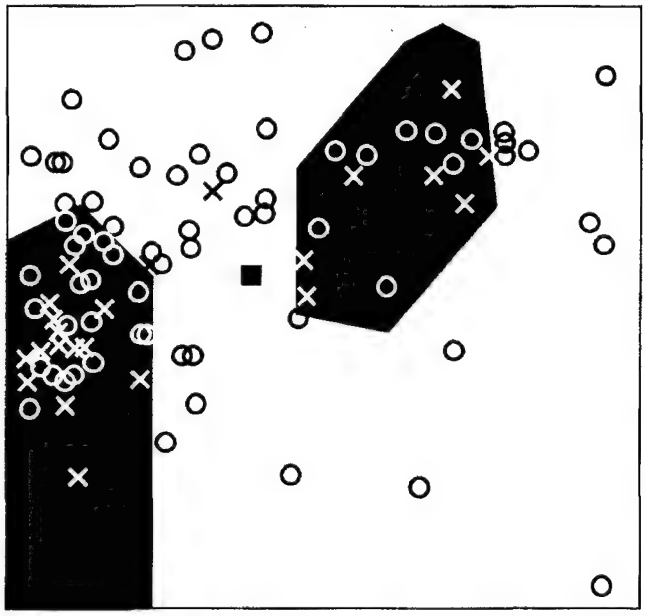

Figure 2. Relational map of design set *D* and the query ROI. Each malignant case is labeled X, and each benign case is labeled O. The query ROI is labeled ■.

A weakness of the mapped-database system is that it does not reveal the quantitative relationships between the mapped feature space and the unmapped features. This weakness is compensated for, however, by the ability of the relational map to cluster visually and diagnostically similar ROIs and by the map's representation of a multidimensional decision surface as a decision curve (or as several disjoint decision curves) in the mapped feature space. The clustering helps the radiologist to find ROIs that are visually similar to the query, and the decision curve helps the radiologist to determine the confidence of the neural network in its recommendations either for or against performing biopsy. Further insight into the relationships between the mapped feature space and the original features can be obtained by making available the numerical values of the original features of each mapped ROI to the radiologist-user.

The user interface presented on the computer monitor is illustrated in Figure 3. This interface guides the radiologist-user through the steps of diagnosis. Identification numbers in this figure (eg, 011318) were constructed so that patients could not be identified from the information in the figure. The mammographic image in the upper left is an enlargement of the ROI

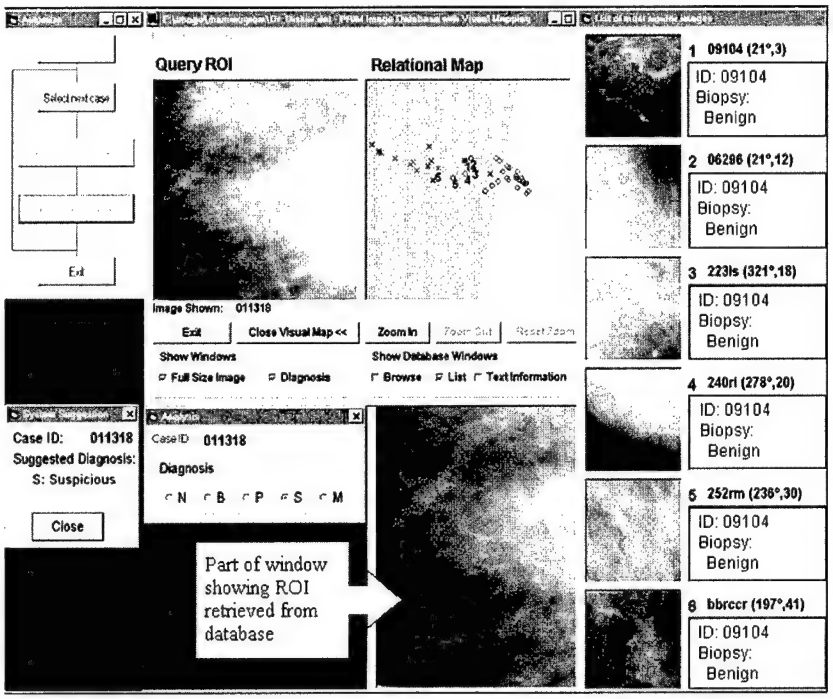

Figure 3. User interface for mammographic diagnosis.

of a query mammogram. Digital magnification and negative-to-positive inversion were provided as options on the user interface. In response to a prompt from the interface, the radiologist first determines an "unaided" diagnosis of this ROI and reports it in the BI-RADS code (26) by clicking N, B, P, S, or M, which denote normal, benign, probably benign, suspicious (possibly malignant), and almost definitely malignant, respectively. In this study, we assumed that N, B, and P corresponded to biopsy not recommended and that S and M corresponded to biopsy recommended. This assumption conformed to the clinical practice at KDMC. We instructed each reader to produce the unaided diagnosis as if it were the final diagnosis for the examination. No time limit was imposed on this diagnosis.

In this study, the diagnostic process began by establishing an unaided diagnosis, which was followed immediately by establishing an aided diagnosis (analogous to double reading). We assumed that the operating point (ie, the subjective decision threshold for a BI-RADS symbol) of the unaided radiologist might be affected by that radiologist's anticipation of an aided diagnosis, but that the receiver operating characteristic (ROC) of the unaided diagnosis was unaffected by that anticipation.

Immediately after the unaided diagnosis was established, the relational map was presented to the radiologist. This map contained the mapped database, mapped query, and distinctively colored decision regions. Thumbnail images of six ROIs near the query in the mapped feature space were presented at the right of the monitor screen. From these images, the radiologist retrieved for review those with a visual appearance that seemed to be most similar to that of the query. This review was facilitated by an enlarged view of the retrieved ROI and the accompanying biopsy reports. On the basis of this interaction, the radiologist selected a BI-RADS score for the ROI. Again, the reader was not restricted by a time limit for establishing this diagnosis, and both magnification and inversion were provided as options on the user interface.

To evaluate the diagnostic improvement provided by the mapped-database diagnostic system, we computed the ROC of each unaided radiologist, of each computer-aided radiologist, and of the computer alone. Each ROC accounted for the BI-RADS responses of the radiologists and for the outcomes of the biopsies. The diagnostic performance of each radiologist was measured by the area A_z under the ROC curve, which is an estimate of the probability for a correct decision in a forced choice between two ROIs, one of which is malignant and the other of which is benign (27). Thus, A_z must lie between a minimum of 0.5 (corresponding to an unbiased random guess) and a maximum of 1 (perfect performance).

We also computed the average performance of the four radiologists when unaided by the mapped-database system and when aided by the mapped-database system. LABMRMC (C.E. Metz, LABMRMC 1.0B, beta version 3, University of

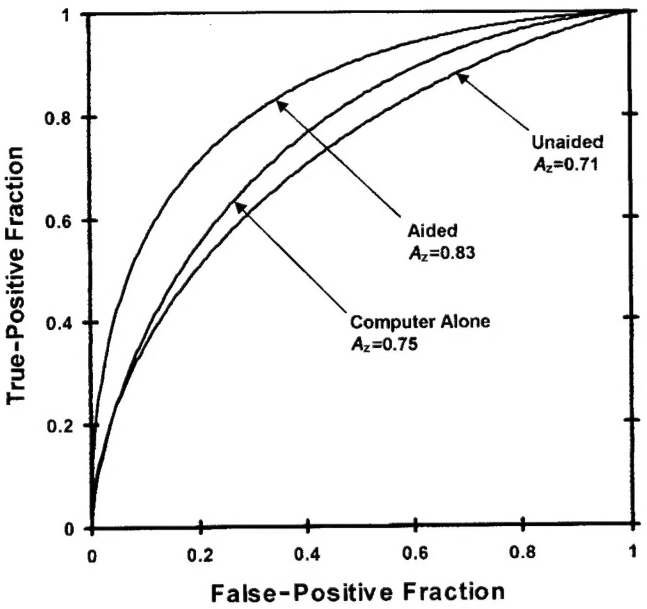

Figure 4. ROC curves for radiologist R_1 and for the computer alone.

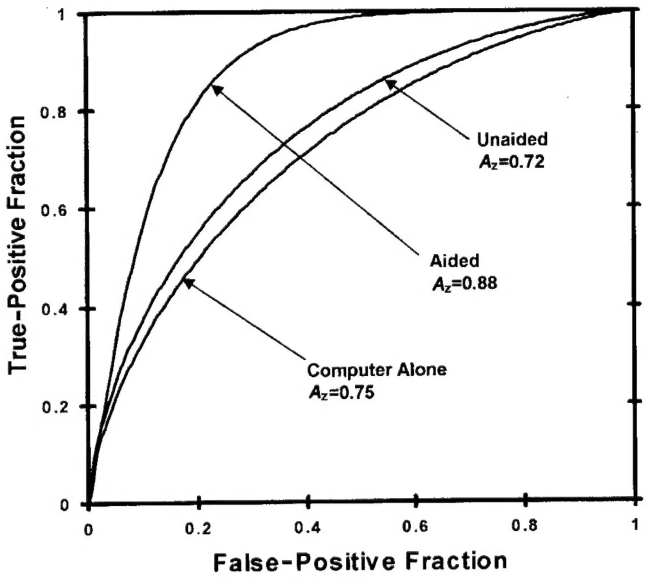

Figure 5. ROC curves for radiologist R_2 and for the computer alone.

Chicago, Chicago, Ill) (28) was employed to calculate the maximum likelihood estimates for the parameters of binormal models and the statistical significance of the change in areas under the ROC curves for the unaided and the aided reading modalities. The ROC curves representing the average performance of the unaided radiologists were computed by averaging their estimated slopes and intercepts in normal deviate space. This same process was also performed for the aided radiologists.

The mapped-database diagnostic system was designed and implemented at the University of California, Irvine, on an IBM-PC–compatible computer with a 66-MHz Intel 486 processor, 32 MB of random access memory, and a 17-inch CTX monitor with 1,280 × 1,024 pixels running on a Microsoft (Redmond, Wash) Windows 95 operating system. The software development environment was Microsoft Visual C++ 4.0 for image-processing functions and Microsoft Visual Basic 5.0 for the user interface. Testing of this system was performed at KDMC on another IBM-PC–compatible computer with a 233-MHz Pentium II processor, 64 MB of random access memory, and a 17-inch monitor (Vivitron; Gateway 2000, Sioux City, SD) with 1,280 × 1,024 pixels running on a Microsoft Windows 95 operating system.

RESULTS

The ROC curves, labeled by their A_z values, are shown in Figures 4–8. The statistical significance of the changes

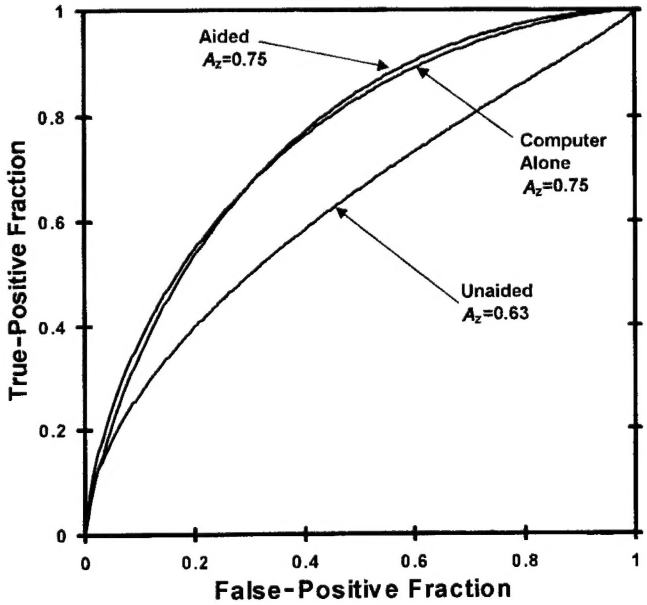

Figure 6. ROC curves for radiologist R_3 and for the computer alone.

in these A_z values is reported in Table 2. The columns of A_z values for the unaided radiologist, the aided radiologist, and the computer alone are labeled A, B, and C, respectively. The column labeled A-B denotes the values of P associated with the increase in A_z obtained by replacing an unaided radiologist with the corresponding aided radiologist. The values of P listed in Table 2 are two-tailed and

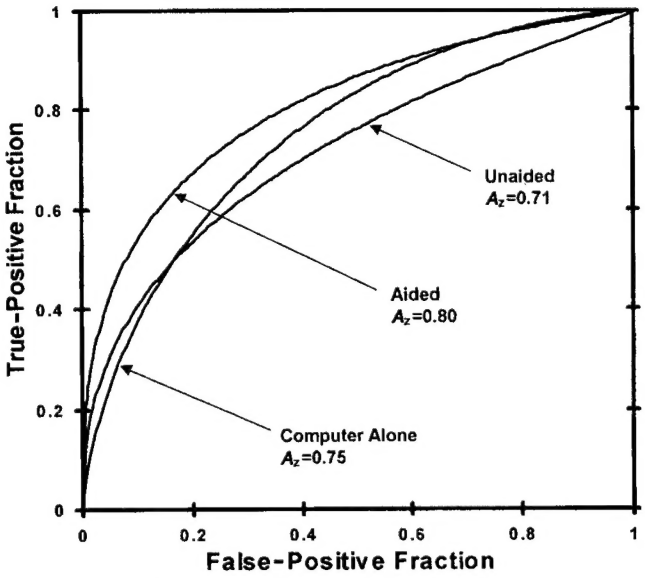

Figure 7. ROC curves for radiologist R_4 and for the computer alone.

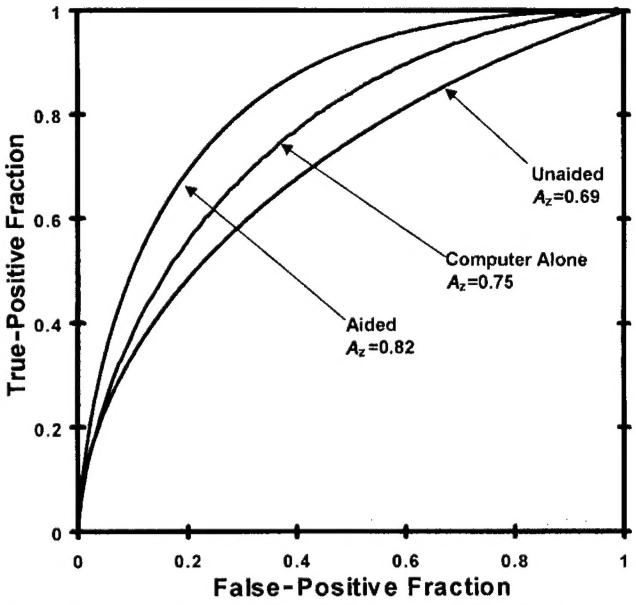

Figure 8. ROC curves for the average performance of the four radiologists.

Table 2
Comparison of ROC Curves for the Unaided Radiologist, the Aided Radiologist, and the Computer Alone

	A_z			P
Reader	A, Unaided	B, Aided	C, Computer Alone	A-B,Two-tailed
R_1	0.7150	0.8354	0.7533	0.0157
R_2	0.7179	0.8814	0.7533	0.0013
R_3	0.6277	0.7538	0.7533	0.0015
R_4	0.7157	0.8077	0.7533	0.0636

were calculated under the assumption that the distribution of each estimated change in A_z, divided by the estimated standard error of that change, arose from a normal distribution. These values of P were computed by using the ROCKIT software (C. E. Metz, ROCKFIT 0.9B, beta version, University of Chicago, Chicago, Ill, 1998).

The information in Figures 4–7 indicates that (*a*) every aided radiologist outperformed the same unaided radiologist, (*b*) no unaided radiologist outperformed the computer alone, and (*c*) three aided radiologists outperformed the computer alone and the fourth aided radiologist (R_3) performed approximately equal to the computer alone. The information in Table 2 indicates that the A_z values of the unaided radiologists ranged from 0.6277 to 0.7179, and that those of the aided radiologists ranged from 0.7538 to 0.8814. The size of the changes in A_z among the radiologists ranged from 0.0920 to 0.1635. Table 2 also indicates that the A-B changes in A_z (ie, unaided-to-aided changes in A_z) were statistically significant at $P < .002$ for radiologists R_2 and R_3, at $P < .02$ for radiologist R_1, and at $P < .07$ for radiologist R_4. After application of the Bonferroni correction for multiple comparisons, these three P bounds became .008, .08, and .28, respectively (29). Other changes in A_z—namely, A-C (ie, unaided–to–computer alone changes) and B-C (ie, aided–to–computer alone changes)—were not statistically significant.

Figure 8 shows the average performance of the four radiologists when unaided by the mapped-database system and when aided by the mapped-database system. Results of the LABMRMC analysis indicate that performance of the aided radiologists, as a group, was statistically superior to that of the unaided radiologists as a group ($P < .05$).

At KDMC, the diagnostic scores S and M are conventionally interpreted as being biopsy recommended, and N, B, and P are interpreted as being biopsy not recommended. In accordance with this convention, we calculated the numbers of negative biopsies and misdiagnosed cancers, as well as the sensitivities and specificities of each radiologist, both aided and unaided by the mapped-database system. These results are shown in Tables 3–5. Tables 3 and 4 show the numbers of recommended benign biopsies and misdiagnosed cancers. Table 5 shows the sensitivities and specificities. The mapped-database diagnostic system helped every radiologist reduce the number of benign biopsies by 40% or more while simultaneously reducing the number of misdiagnosed cancers. All

Table 3
Numbers of Recommended Benign Biopsies for the Unaided Radiologist and the Aided Radiologist

Reader	Unaided Radiologist	Aided Radiologist
R_1	18	11
R_2	15	8
R_3	28	18
R_4	18	10
NN	24	...

Note.—Number of ROIs from benign cases: 57. NN = neural network.

Table 4
Numbers of Misdiagnosed Cancers for the Unaided Radiologist and the Aided Radiologist

Reader	Unaided Radiologist	Aided Radiologist
R_1	11	8
R_2	12	7
R_3	7	4
R_4	8	3
NN	4	...

Note.—Number of ROIs from malignant cases: 23. NN = neural network.

the radiologists also increased both their sensitivities and specificities through their interaction with the mapped-database system. The statistical significances of these increases ranged from $P < .01$ to $P \leq .12$ on the basis of a comparison of proportions (30).

As mentioned, the sensitivities, specificities, and ROCs were calculated on the basis of the 160 abnormal ROIs and the responses of the panel of radiologists to them. The responses of the panel of radiologists to the 20 normal ROIs (the remaining 20 normal ROIs were in the set D_N) were excluded from these calculations, because in this study, the mapped-database diagnostic system was designed only to interpret abnormal ROIs.

DISCUSSION

Figures 4–8 and Tables 2–5 indicate that the diagnostic performances of the aided radiologists were statistically significantly improved compared with those of the unaided radiologists. Table 2 shows that the sizes of these improvements in A_z for the current study are comparable to those in A_z found during a recent study concerning computer-aided characterization of mammographic masses (20).

We are also encouraged by the improved performance of the aided radiologists over that of the computer alone, as indicated in Figures 4, 5, 7, and 8 and in Table 2, although the number of cases was insufficient to prove statistical significance of these improvements. Table 5 shows that the mapped-database diagnostic system enabled substantial increases in specificities and sensitivities for all the radiologists in our panel. We conclude that for ROIs containing microcalcifications, the mapped-database diagnostic system shows promise in helping most radiologists to raise their diagnostic performances substantially over their unaided performances while providing relevant images from a proved database to support the radiologists' aided diagnoses. In particular, these radiologists may achieve substantial reductions in the number of benign biopsies and misdiagnosed cancers.

The levels of postresidency mammographic experience among the radiologists in this study ranged from 29 years to 6 months ($R_1 > R_2 > R_3 > R_4$). Figures 4–7 suggest that all radiologists are likely to benefit substantially from access to the mapped-database diagnostic system regardless of their experience. This is important, because radiologists vary widely in their diagnostic skills—even among those who rate themselves as "experts" (31). Whether the size of the benefit correlates with the amount of experience, however, is not clear from Figures 4–7. (It is interesting that the performance of the aided R_2 exceeded that of the aided R_1, even though the experience of R_1 was greater.)

The results of this study suggest that a properly designed interface between a human reader and a proved database of mammographic images may enable less experienced readers to exceed the performances of unaided, highly skilled readers—without the need for time-consuming training on feature extraction as exemplified by Getty et al (19). Furthermore, our diagnostic system represents an improvement over earlier systems (17,19) by automating the selection of visual features.

This study was limited, however, by the quality of the monitors used for viewing the images, the size and comprehensiveness of the mammographic database, the lack of full-field and earlier views, the restriction of the lesions to microcalcifications, and a possible "reading-order effect" associated with the close succession of unaided and aided diagnoses (32). Our next investigation of the mapped-database diagnostic system will include several enhancements to overcome these limitations. The images will be viewed on state-of-the-art, high-resolution radiographic monitors, and the number of cases will be increased. The tested images will also include full-field craniocaudal and mediolateral oblique or lateral views of each breast, and the lesions

Table 5
Statistical Significance of Changes in Performance

	Unaided Radiologist (%)		Aided Radiologist (%)		Change in Sensitivity		Change in Specificity	
Reader	Sensitivity	Specificity	Sensitivity	Specificity	Change (%)	*P*	Change (%)	*P*
R_1	47.8	73.7	69.6	86.0	+21.8	<.01	+12.3	.12
R_2	65.2	68.4	87.0	82.5	+21.8	<.01	+14.1	<.05
R_3	52.2	68.4	65.2	80.7	+13.0	.09	+12.3	.07
R_4	69.6	50.9	82.6	68.4	+13.0	<.05	+17.5	<.05

will include both masses and microcalcifications. In addition, the aided and unaided diagnoses will be separated by at least 1 month.

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